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Original Communications

THE NEUROVASCULAR SYNDROME PRODUCED BY HYPERABDUCTION OF THE ARMS

THE IMMEDIATE CHANGES PRODUCED IN 150 NORMAL CONTROLS, AND THE EFFECTS ON SOME PERSONS OF PROLONGED HYPERABDUCTION OF THE ARMS, AS IN SLEEPING, AND IN CERTAIN OCCUPATIONS

COLONEL IRVING S. WRIGHT, M.C., ARMY OF THE UNITED STATES

INTERMITTENTLY over a period of many years, attention has been focused on vascular and neurologic syndromes resulting from anatomic anomalies in the neck and shoulder girdle.

The earlier reports[1-11] emphasized for the most part the basic conception that extensions of the transverse processes and cervical ribs arising from the seventh, sixth, or, rarely, the fifth cervical vertebra, may be responsible for pressure on the subclavian artery, the brachial plexus, or both, which, in turn, may result in paresthesias, coldness, impaired circulation, and, in severe cases, gangrene of the fingers. Roentgenograms of the cervical area demonstrate the presence of these bony anomalies in true cases, but it was later observed that this combination of symptoms and signs may develop in the absence of bony abnormalities. Dissection in such cases demonstrated several anatomic patterns, the most common of which are: (a) A tendinous or cartilaginous band extending from, or in the place of, a rudimentary cervical rib and acting in the same manner as its bony counterpart.[16] (b) Abnormal torsion and pinching of the subclavian artery and the brachial plexus as they pass between the anterior and the medial and minimal scalenus muscles above their points of attachment to the first rib.[12-16] (c) An arrangement which permits unusual ease of compression of the subclavian vessels and brachial plexus between the clavicle and the first rib, especially upon backward and downward bracing of the shoulders.[5, 17]

Any of these anatomic patterns may be present without producing symptoms, but may under certain conditions produce the syndrome which has been too loosely classified as the "scalenus anticus syndrome."

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TABLE I

DIFFERENTIAL DIAGNOSIS OF CERTAIN NEUROVASCULAR SYNDROMES OF THE UPPER EXTREMITIES

	CERVICAL RIB SYNDROME	SCALENUS ANTICUS SYNDROME	RUPTURED NUCLEUS PULPOSUS OF THE CERVICAL SPINE	COSTOCLAVICULAR COMPRESSION BY BACKWARD AND DOWNWARD BRACING OF THE SHOULDERS (FALCONER AND WEDDELL)	SYNDROME PRODUCED BY HYPERABDUCTION OF THE ARMS
AGE	Common in early middle life or later	Same	Reported cases mostly in young adults, probably any age	Any	Only young adults have been studied
SEX	Both	Both	Both	Both	Both
SYMPTOMS	Paresthesias, numbness, pain in fingers and hand (ulner distribution most common)	Same, tenderness over scalenus area	Intermittent symptoms; paresthesias, numbness, anesthesias, pain in fingers and hand, pain and tenderness over area of ruptured cervical disc	Paresthesias, numbness, pain in fingers and hand	Paresthesias, numbness, pain in fingers and hand
SIGNS	Cyanosis in adduction of hand, occasional hyperhydrosis	Same	Not striking	Cold, blue hands, tendency to chilblains and "Raynaud's attacks"	Normal color in adduction Pallor on hyperabduction in some cases
GANGRENE	In extreme cases, dry Moderately painful	Same	Never occurs	Arterial thrombosis with gangrene in severe cases	In extreme cases, dry Moderately painful
POSITION AGGRAVATING SYNDROME	Adduction with tension, as in lifting weight	Same, plus turning head away from affected side	Extension of neck, straining, coughing	Backward and downward bracing of shoulders; hyperextension of neck	Hyperabduction of arms
OBLITERATION OF PULSE	Arms in extreme adduction or/and with head turning away from affected side	Same, incidence less common than formerly believed	Never	60 to 70 per cent of normals	Arms in various positions of hyperabduction; 85 to 90 per cent normals

OSCILLOMETRIC READINGS	Confirmatory	Confirmatory	Normal	Confirmatory	Confirmatory
SURFACE TEMPERATURE OF FINGERS AND HAND	Cool in adduction	Same	Normal	Cool if prolonged in aggravating position	Cool in hyperabduction
EVIDENCE OF VENOUS OBSTRUCTION	None	None	None	Pronounced dilation of superficial arm and pectoral veins, especially in infrared photographs	Not pronounced except with primary axillary venous thrombosis. Further study needed
ROENTGENOGRAMS	Cervical ribs unless only rudimentary fibrous bands exist	Negative	Cervical spine: narrow intervertebral spaces *late*. Intraspinous air or radiopaque substances may demonstrate defect in spinal canal	Angle exposures may show asymmetrical thoracic inlet, with evidence of narrowed space in aggravating postures	Negative
VENOGRAMS	Rare, or no abnormalities	Obstruction only if vein is pinched closed on adduction, or turning of head	Normal	Obstruction in some cases Further study indicated	Obstruction only if vein is pinched off on hyperabduction, with or without thrombosis (total experience too limited for final conclusions)
LOCAL ANESTHETIC	No value	If successful, temporary relief	No value	No value	Further studies needed
TREATMENT	Temporary relief in hyperabduction Surgical: excision	Relief on hyperabduction Surgical: severing scalenus anticus muscle	1. Traction, immobilization 2. Surgical procedures: (a) removal of disc, (b) fixation	1. Mild cases, exercises for improvement of postural tone of muscles of shoulder girdle 2. Severe cases, removal of segment of offending rib	Relief in adduction Avoiding posture of hyperabduction

Patients often complain of paresthesias, numbness, and tingling after sleeping or working with their arms in the position of hyperabduction.* Most frequently they change their positions and little attention is paid to these phenomena. Few studies have mentioned the subject. Todd[18] reported an experiment on himself in which he slept with his right arm stretched out almost vertically under his head. This was continued with some interruptions for eight years (1913 to 1921), at which time tingling, loss of sensation, swelling, desquamation, causalgia, and paronychia developed within three months, and affected especially the right thumb and index finger. He stated that the experiment failed to bring forward evidence relating to vascular changes, although the studies reported do not appear very complete in that regard. The syndrome disappeared when he ceased to sleep in this posture. No thorough study of the incidence of these phenomena in normal persons, or of the precise mechanism responsible for it, was made.

During the past five years the author has encountered, in several instances, evidence of marked vascular and neurologic changes produced by prolonged "hyperabduction" of the arms. In this paper, case histories will be presented, followed by the results of a study of 150 "normal" persons for evidence as to whether this mechanism should be considered as abnormal, or as normal, but capable of producing disturbing symptoms under certain conditions. The anatomic mechanism involved in the production of this syndrome will be considered.

CASE REPORTS

CASE 1.—A 37-year-old Jewish male was first seen in July, 1939, with superficial gangrene of the tips of the second and third fingers of the right hand and of the second finger of the left hand. Early trophic changes were found on the tip of the third finger of the left hand. The gangrenous areas were moderately painful, and tender on pressure. Numbness extended throughout the full length of the involved fingers and the right thumb.

The patient had first noticed bilateral numbness and paresthesias of the fingers four months previously. These became progressively more pronounced, extending up the hands and arms. Superficial gangrene appeared at the finger tips, at which time he consulted a physician. No etiological factors could be found, except possibly the smoking of ten cigarettes a day. Roentgenograms showed no cervical ribs. The possibility of thromboangiitis obliterans or Raynaud's syndrome had been considered by the referring physician, but there were certain objections to both. The following points were against a diagnosis of thrombo-

*The term "hyperabduction" is used in this paper to mean that phase of circumduction which brings the arms together above the head (with the elbows flexed or with their long axes corresponding in plane to that of the body). Some degree of external rotation is necessary to achieve this position. Actually, the term hyperabduction, although accepted in anatomic terminology, is not ideal or an entirely logical term, for abduction is movement away from the median plane of the body, and beyond the 90° angle; the arm in so-called hyperabduction actually again approaches the median plane. Other terms are, however, even less satisfactory. For example, the commonly used term "elevation" to indicate this position is inaccurate when the patient is in the supine position. "Extension," which was also considered, has the anatomic connotation of movement of the arms backward from the dependent median plane position. A review of the literature, together with conferences with orthopedists and anatomists, has failed to uncover a completely adequate single term, and hence "hyperabduction" is used by the author with the above qualifications.

angiitis obliterans: (a) the pain and tenderness were much milder than is usual in this disease; (b) the gangrenous areas were of the atrophic, dry type, and were not surrounded by inflamed, angry-looking tissue; (c) the typical color changes of rubor on dependency and pallor on elevation were absent; (d) the ulnar and radial pulses were normal bilaterally; (e) as ascertained by the Allen test,[19] the vessels of the hands functioned satisfactorily; and (f) cessation of smoking had not favorably affected the course of the disease.

Against a diagnosis of Raynaud's syndrome was the complete absence of characteristic precipitation of attacks by cold, emotion, trauma, or other possible etiological factors.

There was no history of taking ergot.

All of these observations were confirmed by the author. In addition, roentgenograms of the vessels of the upper and lower extremities failed to show evidence of calcification. The blood Wassermann reaction was negative. The blood cell count, urine, and blood level of nonprotein nitrogen and sugar were normal.

Oscillometric readings, recorded with the patient in the supine position with his arms by the side, were as follows:

	Right	Left
Upper forearm	4	4
Wrist	2½	2
Hand	1¼	1½

These were considered normal for the instrument used.

The surface temperatures of the fingers were as follows (the readings on the gangrenous fingers were taken 1 cm. from the margin of the gangrene; otherwise, readings were taken at the tips of the fingers):

SURFACE TEMPERATURES

(Room Temperature 72° F. (22° C.)

	Right Hand					Left Hand				
Digits	1	2	3	4	5	1	2	3	4	5
Fahrenheit	90.3°	91.0°	90.8°	89.8°	89.7°	90.1°	90.8°	96.6°	90.0°	89.8°
Centigrade	31.6°	32.7°	32.6°	32.2°	32.1°	31.4°	32.6°	32.5°	31.3°	32.1°

Tests for obliteration of the pulses with the arms hanging down between the knees with the patient in a sitting position, and with the arms flexed forward and abducted laterally parallel to the floor were all normal. There was no palpable diminution in pulse volume, and oscillometric readings showed no decrease.

When, however, the arms were hyperabducted above the head in several positions, it was found that the radial pulses were no longer palpable. Oscillometric readings showed no pulsations in these positions (see Fig. 3 for similar position).

	Right	Left
Upper forearm	0	0
Wrist	0	0
Hand	0	0

This led to the question regarding the possible relation of this phenomenon to the patient's syndrome. Ordinarily, the arms do not remain in such positions long enough to cause any serious ischemia, even if the arterial lumina are thus obliterated. Questioning this patient revealed that, about two months prior to the onset of his symptoms, he had ac-

quired the habit of sleeping with his arms hyperabducted. He stated that the discomfort had never been sufficient to arouse him from sleep or to force him to bring his arms down. He went to sleep at night and awoke in the morning with his arms in essentially the same position. Examination while he was lying in his accustomed position demonstrated that the pulse was absent to palpation and oscillometric study. As far as it was possible to ascertain, his arms and hands were in a state of ischemia, with a relative nutritional deprivation, for seven to nine hours out of each twenty-four.

It was hypothesized that this might well be capable of causing symptoms, and, in an extreme instance, superficial gangrene. The best treatment appeared to be to force the patient to sleep with the arms caudal to the shoulder level. This was achieved with some difficulty (necessitating the tying of his arms loosely so that they would not be abducted above the shoulder level), but there was a prompt therapeutic response. The gangrenous areas were healed in two weeks and the paresthesias disappeared within one month.

Since these observations were made, three additional persons have been seen in Army hospitals with a similar etiological background for existing symptoms, including numbness, paresthesias, and weakness of the hands, but without actual gangrene.

CASE 2.—The symptoms were bilateral and involved the entire hands, with the most marked manifestations in the fingers.

CASE 3.—The symptoms were unilateral, involving only the fingers of the right hand, although the patient slept with both arms equally hyperabducted. This unilateral syndrome will be explained by the studies on 150 so-called normal controls, also reported here.

CASE 4.—The paresthesias and numbness involved the area supplied by the ulnar nerve only, bilaterally.

In each case the numbness was first noticed at the finger tips, and later involved more of the hands and arms.

The reflexes in the upper extremities of all of these patients were normal.

In none of them were the symptoms produced or aggravated by wearing packs or by bracing the shoulders downward or backward.[17]

Examination revealed that the pulse of each affected arm was obliterated when the arm was hyperabducted in the position in which the patient usually slept. The symptoms lasted throughout each day. Curiously, not one of these persons was uncomfortable enough during his sleep to bring his arms down. When these patients did break the habit of sleeping with the arms in the hyperabducted position, their symptoms cleared up within a period of one to four weeks.

Case 5 is reported in detail because it introduces certain additional aspects of this problem.

CASE 5.—This patient was a 27-year-old white soldier who was seen and studied with the cooperation of Captain Harry E. Mock, Jr., in September, 1944. He had been transferred to the hospital at which he was seen with the diagnosis of "possible cervical rib."

History.—One year previously, while lifting a heavy case onto a truck, he was standing in an upright position with his elbows flexed at 80 degrees when the case slipped and "jerked" his right arm at the

shoulder joint. Thereafter he had pain deep in the shoulder joint which made it impossible for him to raise his arm from his side. He recalled pain in the anterior axillary fold, but this was not the site of major discomfort. He was asymptomatic after three weeks. About six weeks after the original injury he again suffered similar pain and disability after hitting an opponent while boxing. The pain in the anterior axillary fold was a more striking feature this time. A lump the size of his fist developed in the scapular region on the posterior surface of the shoulder. This slowly subsided, but, after the second injury, he continued to feel as if his shoulder and upper arm were "going to sleep," and constantly experienced a sensation of heaviness in the region of his shoulder. During the preceding month this condition had grown progressively worse. He had noted increased numbness along the ulnar side of the forearm and hand, involving the fourth and fifth fingers.

For years prior to his accidents this patient had frequently slept with his hands under his head as a pillow. He had experienced paresthesias, but not to a serious degree. About two weeks after his second injury he slept in this position and was unable to move his right arm upon awakening. It was necessary to lift it with his left hand, and it was several hours before he could use it.

Physical Examination.—The patient was a stocky, heavily muscled, 27-year-old man. There were no significant abnormalities unrelated to the problem under discussion. The blood pressure in the right arm was 128/66, and in the left arm, 128/68.

Inspection revealed no abnormalities. There was no engorgement of the collateral veins of the right shoulder. With the arm in a dependent position the skin was of normal color, texture, and temperature as compared with the left upper extremity. When, however, the arms were hyperabducted, the right hand blanched and later flushed, whereas the left hand retained a normal color. There was no limitation of motion of the shoulder, elbow, or wrist joints. No crepitus could be felt in the right shoulder. Measurements revealed that the arms were essentially equal in size.

Testing the upper extremities for sensation to pin prick revealed a variable pattern of decreased sensation on the right side over the posterior aspect of the shoulder, the lateral side of the arm, the ulnar side of the forearm and hand, and the entire fifth finger and ulnar side of the fourth finger. The deep reflexes were normal bilaterally.

The right radial and brachial pulses were obliterated by the following procedures:

1. Abducting the arm laterally 45 degrees.
2. Abducting the arm anterolaterally to a 90-degree angle.
3. Abducting the arm posterolaterally to a 45-degree angle.
4. Abducting the arm in any of the above directions to just below the level where the pulse was obliterated, and then having the patient rotate his head to the left.
5. By having the patient contract his right pectoralis major and minor muscle group with the arm in any position.
6. By having the patient inspire deeply and hold his breath.
7. By having the patient force his shoulders backward and downward.

Elevation of the shoulder or contraction of shoulder muscles other than the pectoralis group would not result in obliteration of the pulse.

By contrast, the pulse in the left arm could be obliterated only by having the patient hyperabduct his arm above a 150-degree angle, or by having him force his shoulders backward and downward.

Injection of a 1 per cent solution of procaine in the region of the scalenus anticus muscle failed to prevent the obliteration of the pulse by the above-mentioned maneuvers, although the procedure was subject to the inevitable factors of uncertainty in this area. Roentgenologic studies of the right shoulder girdle, chest, and cervical spine showed nothing abnormal.

The mechanisms involved in the symptomatology and the obliteration of the pulse in this case were obviously more complex than in the others, and will be considered later in this paper.

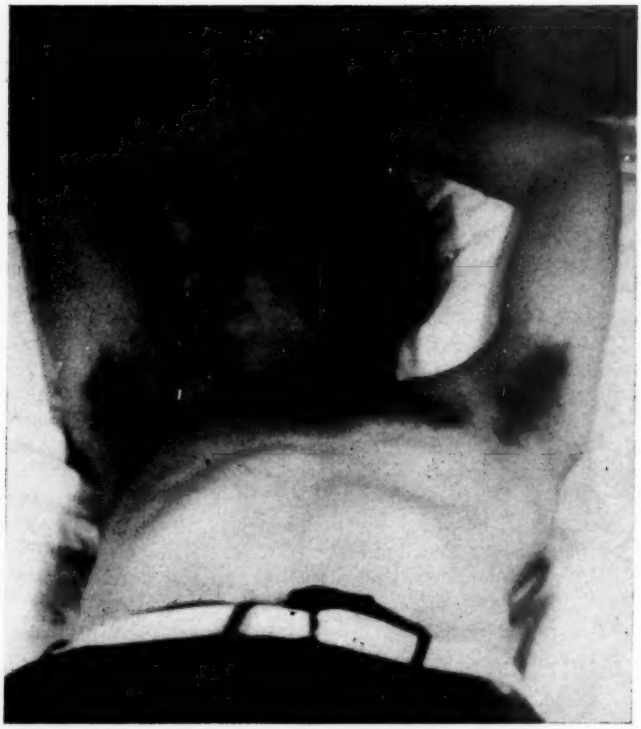

Fig. 1.—Sleeping position frequently seen in hospital wards, in which obliteration of the pulse and overstretching of the nerve trunks may occur.

COMMENTS

In each of the first five cases, the syndrome had previously been misinterpreted. The following possibilities had been considered: Raynaud's syndrome, thromboangiitis obliterans, intrinsic or extrinsic tumor of the cervical cord, ruptured nucleus pulposus in the cervical area, infectious polyneuritis, ulnar and median nerve injury, cervical rib, and scalenus anticus syndrome.

This gave rise to the following questions:

1. What is the incidence of obstruction of the major arteries to the upper extremities as a result of hyperabducting the arms in various positions?
2. Is this abnormal or normal?

3. What is the mechanism by which this syndrome is produced?

4. What percentage of persons recognize symptoms which arise from assuming this position and tend to protect themselves against it?

5. Can sensory changes be produced by assuming this position in the absence of obliteration of the arterial pulsation?

Studies were undertaken to answer these and additional questions.

STUDIES ON NORMAL ADULTS

One hundred fifty young adults, considered to be normal with regard to this syndrome, were examined with the cooperation of Lieutenant Colonel Austin B. Chinn and Major Roscoe Millet. Observations were made as follows:

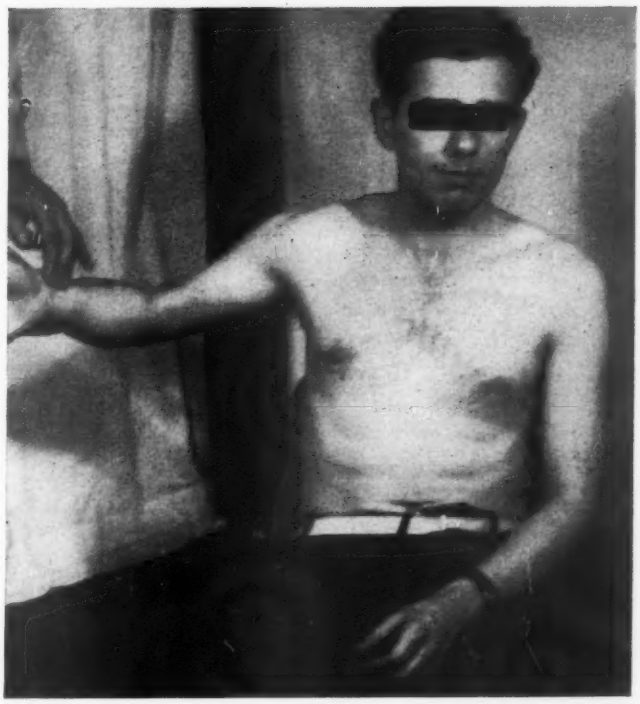

Fig. 2.—Patient in position for test. Arm abducted anteriorly and laterally. The pulse is strong and is easily felt in this position.

The patient was seated in a small, straight-backed chair. The radial pulse was checked for its presence and strength in positions below shoulder level (Fig. 2). Each arm, in turn, was hyperabducted with the examiner's fingers on the radial pulse (Fig. 3). Subjects whose vessels were obstructed easily were, in fifteen instances, checked by having them lie in bed and hyperabduct their arms (Fig. 4). Notations were made as to (1) whether the pulse could be obliterated in any position; (2) whether this was easy or difficult to accomplish (in other words, whether there were many points or only one point at which this

could be achieved); (3) the position at which it first disappeared as the arm was hyperabducted; (4) whether deep inspiration could produce obstruction with the arm held in a marginal position (i.e., one in which slight movement would open or shut off the arteries); (5) whether the incidence of this sign was influenced by muscular development; (6) whether neurologic symptoms could be produced within two minutes

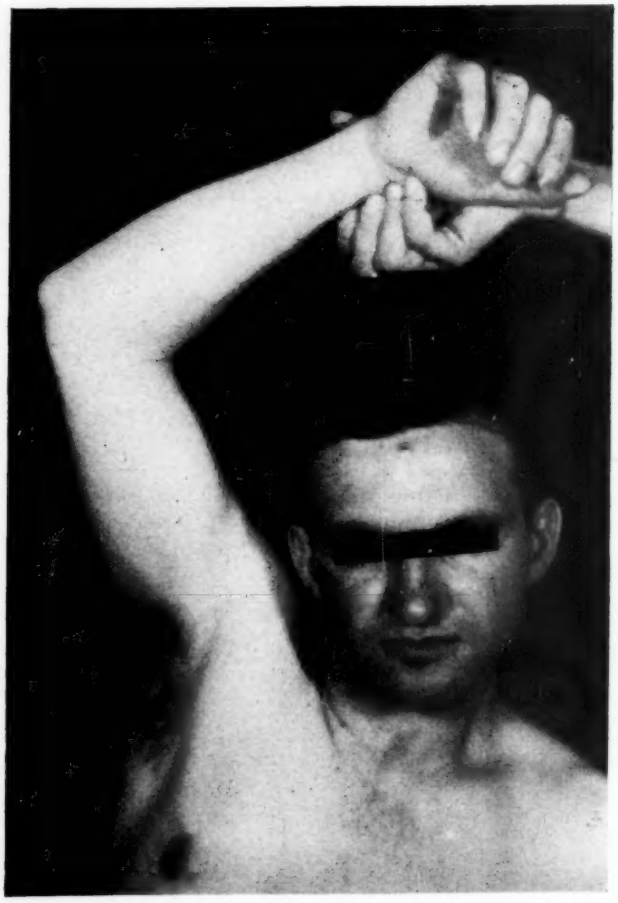

Fig. 3.—Second position for test. In many instances the pulse is completely obliterated by simply hyperabducting the arm to this or a similar position (1 plus or 2 plus difficulty). In others, it is more difficult to ascertain an exact position at which the pulse disappears (2 plus or 4 plus difficulty). In the third group the pulse cannot be obliterated in any position.

without interference with the major circulation, as evidenced by absence of change in the pulse. Questionable observations were checked by more than one examiner.

The results of this study were as follows:

In one hundred twenty-five of one hundred fifty "normal" subjects (83.3 per cent), obliteration of the right arm pulse could be produced by hyperabduction of the right arm above the head (Fig. 3). In one

hundred twenty-four of the one hundred fifty (82 per cent) "normal" persons, obliteration of the left arm pulse could be produced by hyperabduction of the left arm above the head. Obliteration of the radial pulse paralleled that of the brachial pulse.

There was considerable variation in the difficulty encountered in producing this obliteration. In some instances it could be produced by merely hyperabducting the arm, and sometimes occurred before the arm reached 180 degrees. In others, it was necessary to apply moderate stress to the arm, forcing it posteriorly and moving it about into different positions in order to find one at which the pulse was obliterated.

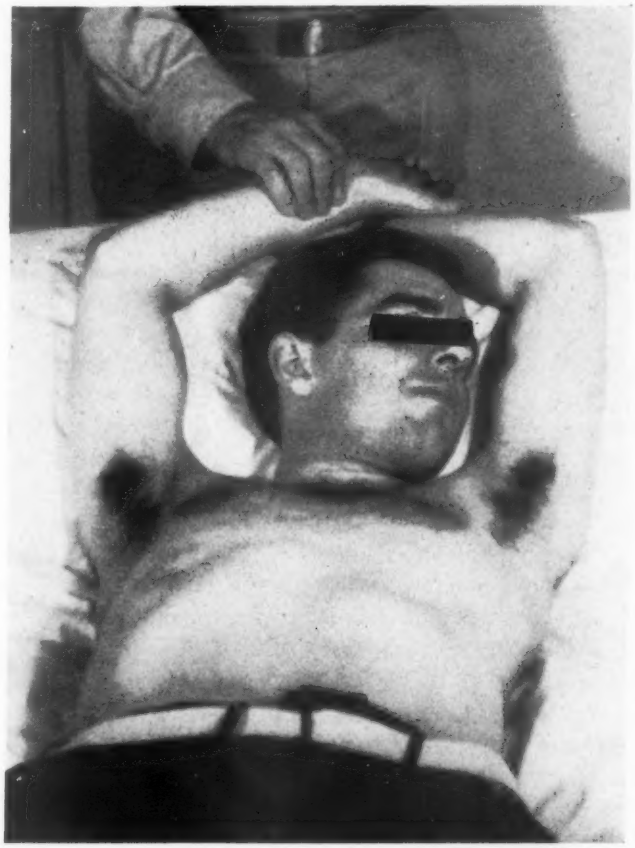

Fig. 4.—Third position for test. If obliteration occurs in second position, a check is made to ascertain whether the pulse is absent in the position in which patient usually sleeps. This may be modified by using other positions under suspicion, such as those used in overhead occupations, e.g., painting ceilings, riveting, etc.

These variations in difficulty were graded as 1 to 4 plus, i.e., 1 plus was easy, and 4 plus was difficult, but possible. The results are given in Table II.

It will be noted that in 94, or 62 per cent, obliteration of the right arm pulse, and in 95, or 63 per cent, obliteration of the left arm pulse

TABLE II

RESULTS OF A STUDY OF OBLITERATION OF THE PULSES IN THE MAJOR ARTERIES OF THE ARMS OF 150 NORMAL SUBJECTS PRODUCED BY HYPERABDUCTION OF THE ARMS

DIFFICULTY	RIGHT ARM		LEFT ARM	
	NUMBER OBLITERATED	PERCENTAGE	NUMBER OBLITERATED	PERCENTAGE
1 plus	49	32	48	32
2 plus	45	30	47	31
3 plus	23	15	22	14
4 plus	8	5	7	4
Total	125	83	124	82

was *easily* produced by hyperabduction of the corresponding arm, as described. In only eleven of the one hundred fifty subjects (7.4 per cent) could no obliteration be produced in either arm. Neurologic symptoms, including paresthesias, were produced in two cases (in one in the left, and in one in the right) within two minutes, in the *absence* of obliteration of the pulse.

The frequency of obliteration of the pulse was much higher than anticipated, and the facts certainly warrant the conclusion that the anatomic arrangement is a normal one (in that it occurs in a very high percentage of persons) which, under specific conditions, may produce a specific syndrome. This is important because this position of hyperabduction is today being widely, but erroneously, used as a test for the scalenus anticus syndrome. The scaleni are relaxed rather than tensed in this position. As was pointed out by Oehsner, Gage, and DeBakey,[15] this position frequently relieves the pain in the scalenus anticus syndrome.

Observations were made as to whether there was any correlation between the degree of muscular development and the ease with which the pulse could be obliterated. No such correlation could be established, except that obliteration of the pulse was very difficult, and frequently impossible, to produce by this method in the "loose jointed" type of person.

Eight subjects could block their pulses by muscular contraction in the marginal position (the position in which a slight movement of the arm would obliterate or restore the pulse). The author has in the past seen numerous persons who could do this in any position by contraction of the pectoralis major and minor group.

In three instances, the pulse could be obliterated in the marginal positions by deep respiration. In two, however, the pulse was definitely made more prominent by deep respiration.

Questioning revealed that thirteen of the one hundred fifty subjects frequently slept with their arms hyperabducted, usually with the elbows somewhat flexed. Six of these slept comfortably in this position. In these, obliteration could be produced only with difficulty, and not in the position in which they usually slept. Seven frequently fell asleep with their arms hyperabducted in similar positions, but soon developed suf-

ficient discomfort to bring their arms down below shoulder level. In six of these subjects, obliteration of the pulses was easy to accomplish, and occurred in the sleeping position which produced the symptoms. One developed numbness in the right hand when tested by this procedure, without obliteration of the pulse.

It has since been noted that, in certain instances, the pulse may be present intermittently. In a position which at first produces obstruction, the pulse may suddenly become strong—to remain, or to disappear as suddenly. It has also been noted that the position of the head may sometimes affect the obliteration of the pulse. Turning the head toward, or away from, the arm being tested may open or close the subclavian-axillary artery. In this group the scalenus muscles may play an important part. Although the direction in which it is necessary to turn the head to produce obliteration is usually constant for one subject, it varies with different persons, e.g., in some, obliteration is produced by turning the head toward the arm being tested, in others by turning the head away from this arm. Flexing the head and neck reduces the incidence of obliteration. Hyperextending increases the incidence. This will be discussed later in this paper. Exact statistical data on the occurrence of these phenomena, which were observed more recently, are not available.

A CONSIDERATION OF THE ANATOMIC MECHANISM WHICH PRODUCES THIS SYNDROME

The frequency with which obliteration of the pulse and neurologic symptoms could be produced in the series of "normal" subjects indicates that the mechanism cannot be based on a structural abnormality, such as a cervical rib or the scalenus anticus syndrome.

The pathologic changes must result from prolonged occlusion of the arterial supply and damage to the nerve trunks caused by stretching, pinching, prolonged ischemia, or all three. Pathologic changes are relatively uncommon because (1) only a small portion of the population sleep or work with their arms hyperabducted for long periods of tim (as in painting a ceiling); (2) most of these will change their position by bringing their arms down below shoulder level when discomfort develops; and (3) in many the arteries are obstructed or the nerves stretched excessively only in certain specific positions, so that, ordinarily, because of frequent changes in posture, the patients do not develop the syndrome even while they sleep with their arms hyperabducted.

The present knowledge of this phenomenon permits only preliminary deductions regarding mechanisms involved.

A review of the anatomic arrangement, with dissections, reveals that there may be variations in the mechanisms responsible for this syndrome in different persons, and even in the same person, as the arms change position. Two points of torsion, stretching, and pinching, operating either alone or jointly, appear to play the major roles in most cases. One is the point at which the subclavian artery and vein (at the seg-

ment of transition into the axillary artery and vein) and the main trunks of the brachial plexus pass posterior to the pectoralis minor, just beneath the coracoid process (Fig. 7). They are well protected in adduction (Fig. 5), but when the arm is hyperabducted they are stretched around and underneath the coracoid process. By the same action the pectoralis minor is drawn tight (Figs. 6 and 7). This double action results in different degrees of stretching and pinching of the artery, vein, and nerves in different persons. Another point where pressure and torsion may be produced by certain positions of the arms and shoulders is found where the artery, vein, and plexus pass between the clavicle and

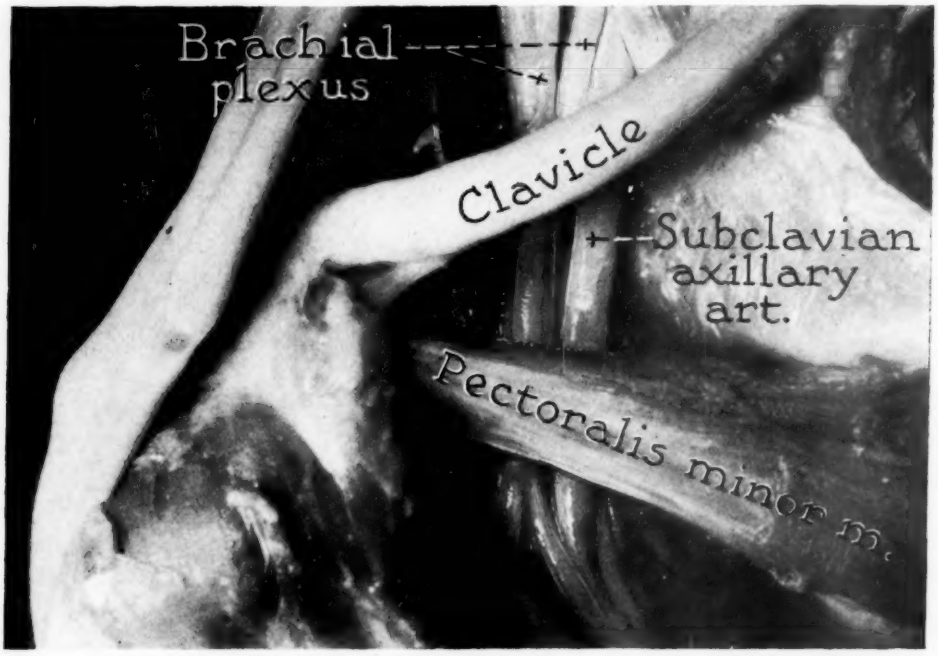

Fig. 5.—Photograph showing relations of brachial plexus and subclavian-axillary artery with the arm in a position of relaxed abduction. They are under no tension or pressure.

the first rib (Fig. 6). Eden[20] described a case (Case 3) with a normal first rib in which obliteration of the pulse occurred as a result of this mechanism when the arm was abducted. Although his patient had severe symptoms, there is no definite history of prolonged maintenance of this posture, either at work or asleep. This was further admirably described by Falconer and Weddell[17] in reference to a syndrome produced by having the patients force their shoulders backward and downward, or by hyperextension of the neck. These movements result in pinching of the vessels and the plexus between the anterior surface of the first rib and the posterior surface of the clavicle. They demonstrated that this pinching, which may result in obliteration of the pulse and

sensory neurologic symptoms, is also a normal, or at least a very common, phenomenon, for it could be produced in twenty-five of fifty men, and thirty of fifty women. In severe cases, relief could be achieved only by preventing the pinching by means of an appropriate surgical procedure.

In studying the syndrome produced by hyperabduction, it has been found that, in certain positions and in certain instances, costoclavicular compression of the subclavian vessels and plexus plays an important role. Through the cooperation of Major Sylvan Moolten, it has been

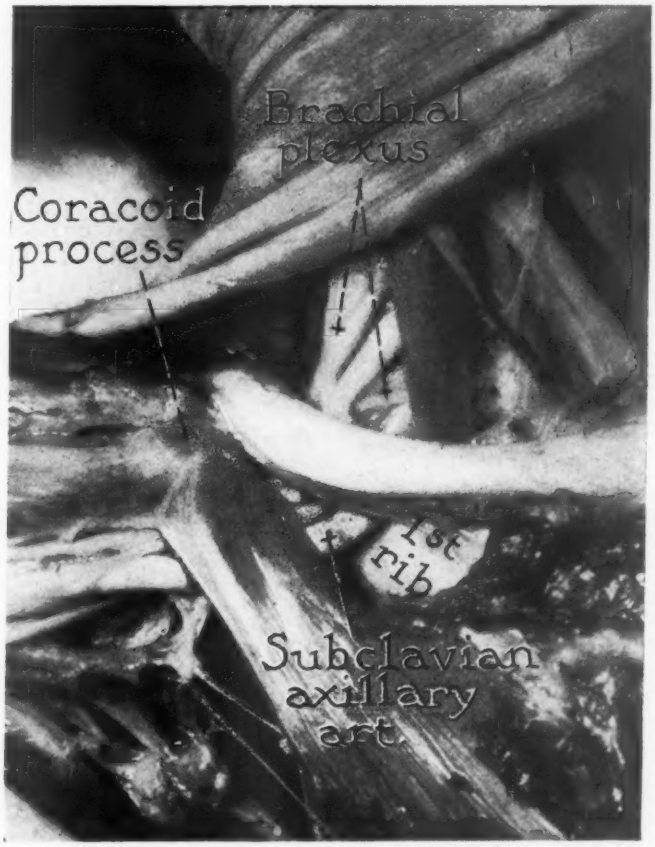

Fig. 6.—Photograph showing relations of brachial plexus and subclavian-axillary artery with the arm in hyperabduction. In many instances in this position the vessels and nerves are stretched and subject to torsion as they pass beneath the coracoid process and behind the pectoralis minor muscle. Marked torsion and pinching may also take place between the clavicle and the first rib.

clearly demonstrated that, under these conditions, there may be a marked reduction in the width of the space between the clavicle and the first rib. The brachial plexus can be seen to become twisted and flattened out into its component cords by this pressure; at the same time, the subclavian artery is pushed downward and forward, and is compressed (Fig. 6). This mechanism may have played a major part in

the obliteration of the pulses of the normal subjects in our series whose pulses could be obliterated only with difficulty, and with backward pressure, as well as hyperabduction. This appeared to play an important role in Case 5, in which the pulse disappeared on both sides after backward and downward movement of the shoulders. The subcoracoid-pectoralis minor syndrome appeared to play a major role in the obliteration of the pulse caused by hyperabduction, for it occurred when the arm was abducted anterolaterally to 90 degrees, a position in

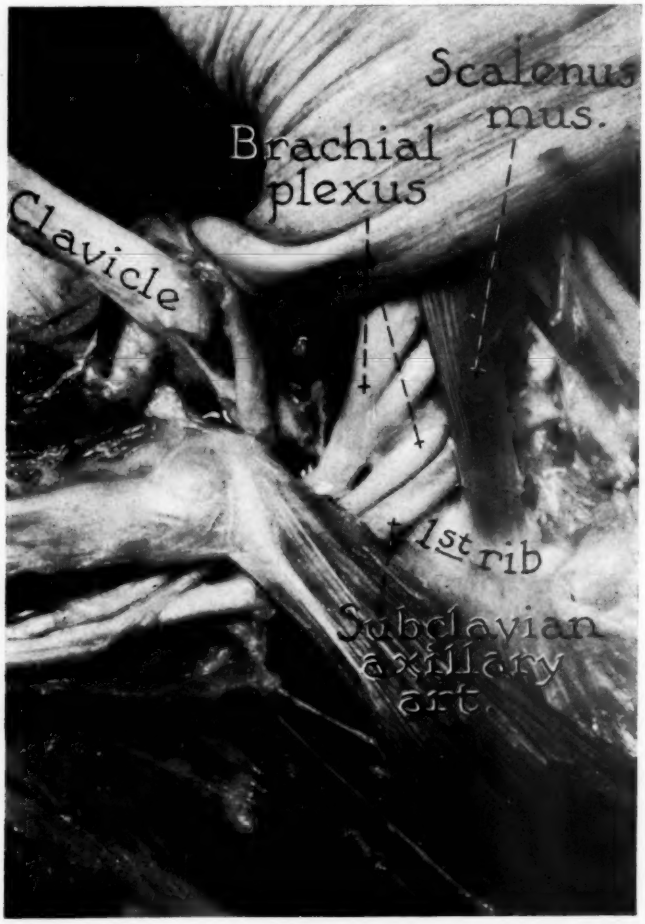

Fig. 7.—With the arm in hyperabduction this illustrates the relationship of the brachial plexus and subclavian-axillary artery to the first rib, coracoid process, anterior scalenus muscle, and pectoralis minor muscle. The clavicle has been lifted out of position.

which the costoclavicular space is at a wide phase. The reason for the pronounced aggravation of this syndrome in the right arm after the injuries must await solution, if and when the area is explored surgically.

Other anatomic stresses and pressures in this extremely complex portion of the body may play some part in this phenomenon in certain

instances. Some of these have been well described by Wartenberg[22] in his discussion of "Brachialgia Statica Paresthetica," or nocturnal arm dysesthesias, which occur independent of hyperabduction.

The stretching or pinching of the nerve trunks probably produces the immediate paresthesias. Ischemia due to impaired blood supply to the nerves may play a part after prolonged hyperabduction. Violent hyperabduction can, as is well recognized, produce paralysis by severe stretching or tearing of some of the brachial plexus trunks.

In addition to the difference in structural relationships, the wide range in reactions to the same positions may depend in part on the great variation in rate of impairment of nerve conduction which follows compression of short segments of peripheral nerve. In view of the studies of Denny-Brown and Brenner,[21] we have attributed this to uneven pressure gradients in the nerve bundles, with consequent variation in the degree of ischemia because of the escape of some small vessels. It is thought that such a relationship is an expression of corresponding relative degrees of ischemia, and not a direct consequence of pressure on nerve fibers.

The fact that tingling and numbness began peripherally and progressed centrally in our cases is in agreement with the principle of centripetal paralysis as observed and formulated by Lewis, Pickering, and Rothschild.[23] They found that the sensations of cold and heat, and also muscular power, were subject to the same laws of centripetal paralysis after the production of ischemia by the use of a blood pressure cuff. The numbness which develops in the finger tips is not due to a process in the finger tips themselves, but rather to changes in those portions of the nerves that lead to the finger tips and which have been rendered ischemic. In their experiments, the amount of blood leakage was distinctly less than in our cases, in which only the subclavian axillary vessels are occluded, and the many collateral vessels of the shoulder may function fairly freely. The nerves of the brachial plexus are nevertheless subject to stretching and pinching, and are therefore at least locally subject to ischemia. The ulnar trunk in the axillary area, since it is the lowest one, is the most vulnerable to damage by stretching of this order, and this corresponds with the occurrence of paresthesias in the ulnar distribution in some of our cases.

The local gangrene of the tissues at the finger tips in Case 1 was, in our belief, the result of prolonged ischemia. It is thought that some blood must leak through the main vessels either continuously or intermittently, for otherwise massive thrombosis would probably occur. Collateral vessels must have contributed to the nutrition of the extremities in all of the cases reported.

Although none of the patients herein reported suffered from primary axillary venous thrombosis, it is possible that the same mechanism may have been responsible for its occurrence in patients who have developed

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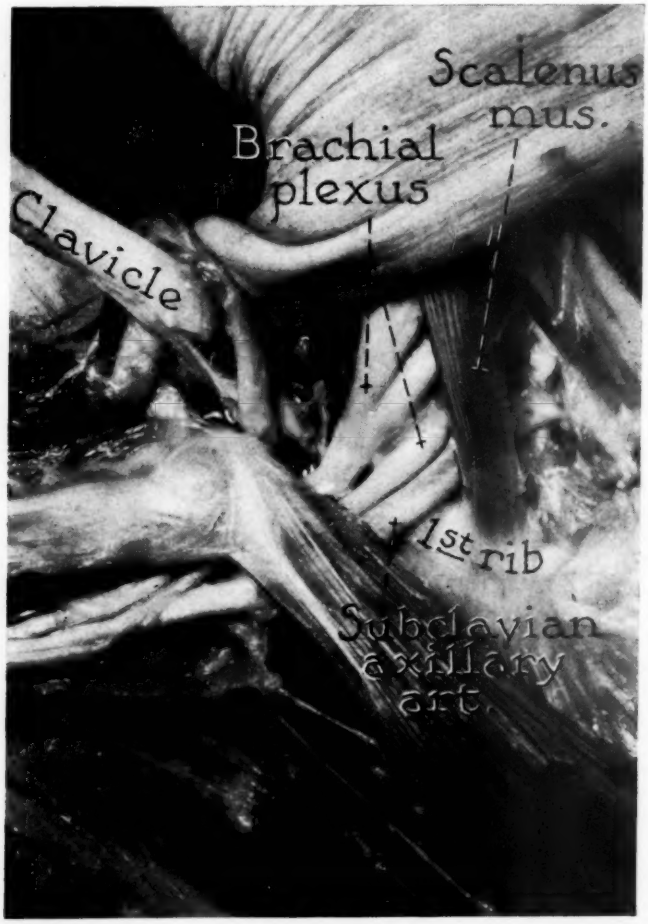

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Although none of the patients herein reported suffered from primary axillary venous thrombosis, it is possible that the same mechanism may have been responsible for its occurrence in patients who have developed

it after horizontal bar exercises or prolonged hyperabduction of the arms while doing up the hair. Venographic studies will doubtless be of interest. These are contemplated.

SUMMARY AND CONCLUSIONS

1. A neurovascular syndrome which is produced by hyperabduction of the arms is described.

2. This is capable of producing gangrene secondary to occlusion of the subclavian artery, and neurologic sensory complaints probably secondary to stretching, and ischemia of the brachial plexus trunks.

3. There are two zones of stretching, torsion, and pinching which contribute to the production of this syndrome: (a) the point at which the axillary-subclavian vessels and the trunks of the brachial plexus pass posterior to the pectoralis minor muscle and beneath the coracoid process; and (b) the point at which the subclavian vessels and the trunks of the plexus pass between the clavicle and the first rib.

4. Further anatomic and functional studies of these and other mechanisms which may contribute to the production of this syndrome will be highly desirable.

5. The first four patients reported herein developed their syndromes as a result of prolonged sleeping in the supine position with their arms hyperabducted; in each case this resulted in arterial occlusion or stretching of the involved nerve trunks. In Case 5 the symptoms were aggravated by a double injury involving the right shoulder. In additional cases, to be reported later, the syndrome has developed as a result of occupational hyperabduction.

6. Data are presented to demonstrate that occlusion of the subclavian artery by hyperabduction of the arms is a normal phenomenon. Most persons will avoid prolonged hyperabduction because of the symptoms produced.

7. It is recommended that persons whose pulses can be occluded in the hyperabducted position refrain from sleeping or working with their arms in that position.

8. It is also recommended that special attention be paid to the state of the pulse and complaints of paresthesias and numbness from patients whose arms are in hyperabduction on operating tables or in splints or casts, in order to avoid the neurovascular complications which occasionally occur as a result of neglect of this principle.

9. This report is published in the belief that calling attention to this syndrome will lead to correct diagnoses in the future, so that patients may be advised regarding the proper treatment for the majority, namely, sleeping with the arms in safe positions, or, in cases of occupational hyperabduction, changing occupations.

10. In a few cases in which the costoclavicular syndrome is dominant, surgical treatment may be necessary.

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MOMENTARY ATRIAL ELECTRICAL AXES

II. Atrial Flutter, Atrial Fibrillation, and Paroxysmal Tachycardia

George M. Decherd, M.D., Arthur Ruskin, M.D., and George Herrmann, M.D.
Galveston, Texas

WE HAVE long been interested in the supposedly unusual combination of paroxysmal atrial tachycardia and atrioventricular block, and have recently directed attention to the unexpected frequency with which block occurs during paroxysms.[1] We were also impressed with the fact that these same patients showed, relatively often, closely associated attacks of atrial flutter or fibrillation.[2] Several patients showed all three types of atrial mechanism disturbance in the course of a few hours or days. This logically led us and others[3] to suppose that the fundamental mechanisms of these three disturbances might be closely related. The present report describes an effort to justify such an inference by clinical experiment.

Barker, Wilson, and Johnston,[4] reporting similar observations, have been led to similar conclusions. Their data led them rationally to the conclusion that paroxysmal atrial tachycardia is the result of a circus rhythm in the atria, the path of which passes through one of the specialized atrial nodes. That this might be true appears to have been suggested first by Iliescu and Sebastiani;[5] more recently, Ashman and Hull[6] have accepted this explanation for some cases, at least, of paroxysmal tachycardia.

The recent paper of Barker, Wilson, and Johnston[4] contains a summary of the available evidence bearing on the point, and it must be confessed that from this evidence one may reasonably conclude that paroxysmal tachycardia may be due to a circus mechanism. They support their opinion by citing data relating to the electrocardiographic form of the atrial complex, the constancy of the rate and its usual failure to be influenced by exercise, the effect of reflex vagal stimulation, the mode of action of quinidine and digitalis, the occasional occurrence of A-V block and of alternation of the P-P cycle length, and the less common close association with atrial flutter or fibrillation.

A circus mechanism might theoretically account quite satisfactorily for most of the known characteristics of paroxysmal tachycardia, as Barker and his associates have indicated. However, actual proof is thus far lacking that such a mechanism does exist. The clinical ex-

From the Cardiovascular Service of the John Sealy Hospital, and the Department of Medicine, University of Texas School of Medicine, Galveston.
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periments to be described below represent an attempt to put this question to the actual test. We recognize fully the theoretical, as well as the practical, limitations of the method which we have employed. We feel, however, that the results themselves support the validity of the method, at least for the purposes for which we have utilized it.

In a preceding paper[7] we described the use of electrocardiograms taken in three planes on the chest, and the derivation from them of curves and three-dimensional figures representing the momentary directional change of the consecutive atrial electrical axes. It is, in effect, a slight modification of the method originally employed by Lewis, Drury, and Iliescu[8] in their demonstration of the presence of a circus movement in atrial flutter and fibrillation. Our purpose in making this study has been (1) to reproduce the results obtained by Lewis, et al., in cases of flutter and fibrillation, and (2) to subject patients with paroxysmal tachycardia to the same type of clinical study. The curves obtained have been compared with those obtained from patients showing sinus rhythm. Some of the data have been briefly discussed elsewhere.[9] Barker, et al.,[4] have pointed out the similarities between paroxysmal tachycardia with A-V block and flutter, and have also indicated the differences. Certainly it is in these cases of tachycardia with A-V block that there is most often an associated flutter or fibrillation.[2] It is also precisely these cases which are most readily studied by Lewis' method as we have employed it, for in them some of the P waves are isolated, and are not superimposed on the preceding QRS-T complexes.

EXPERIMENTAL RESULTS

Atrial Flutter.—Although the disciples of Rothberger[10] adhere to the belief that flutter and fibrillation are the result of rapid stimuli arising from parasystolic foci, there has been wide acceptance of the concept developed extensively by Lewis, viz., that the cause of these disturbances of mechanism is movement of the impulse through a circular pathway, which may be regular or irregular, respectively. On the basis of data from experimental flutter, and from one case of flutter in man, Lewis believed that in the usual cases of clinical flutter the circus movement passed around the mouths of the venae cavae. We have constructed Fig. 1, *a*, from Lewis' data,[8] after plotting the curves in the three planes by the procedure previously outlined. In addition, we have studied four cases of flutter of our own, and illustrate the movement of the momentary electrical axes in two of them in Fig. 1, *b* and *c*.

We adopted Lewis' method of choosing a base line in those cases in which there is continuous electrical activity of the atrium, namely, a line drawn midway through the undulations of the string. Lewis[8] accepted this procedure and demonstrated a satisfactory agreement

with the Einthoven hypothesis of the values thus derived. Inasmuch as we were able to record only two leads at one time, it was impossible to trace off the three leads as though they were recorded simultaneously, particularly in atrial fibrillation, in which there is no cyclic repetition of the waves. Lewis presented his data schematically in the form of a ring, in which the direction of movement is clockwise when viewed in the sagittal plane, and counterclockwise in the horizontal and frontal planes.

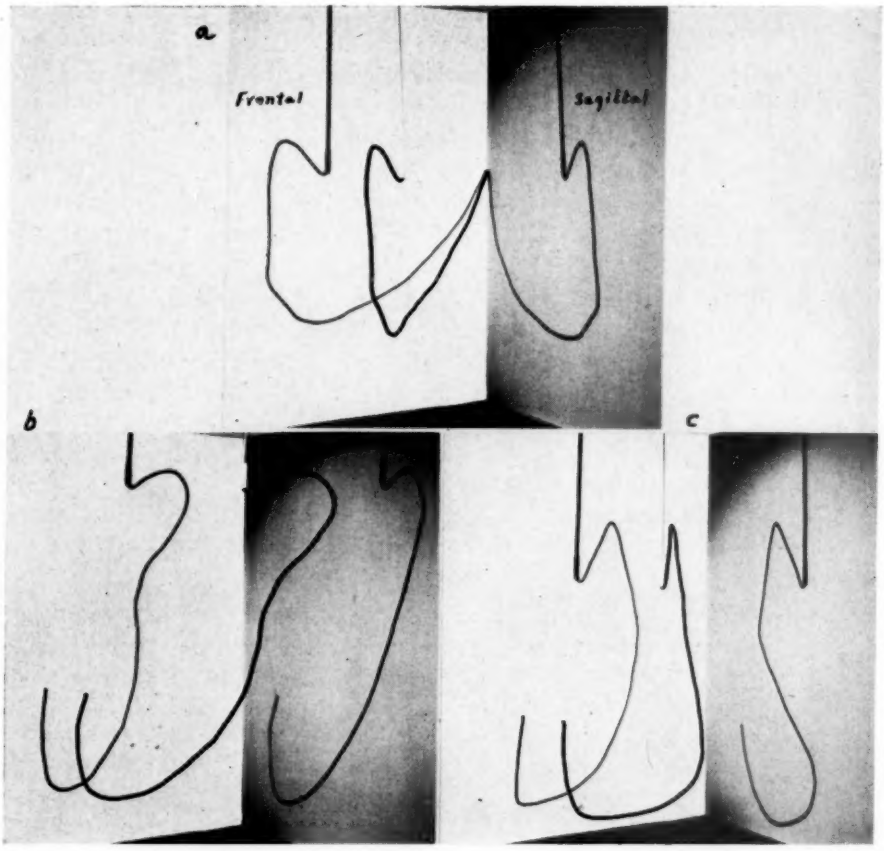

Fig. 1.—*a*, Model constructed from Lewis' data on flutter. *b* and *c*, Our own cases of flutter.

In the first case of our own which is illustrated (J. L., Fig. 1, *b*), the direction of rotation of the axes is clockwise in the sagittal and frontal planes, and counterclockwise in the horizontal plane. In the second case (J. P., Fig. 1, *c*), movement is in a clockwise direction in the frontal plane and counterclockwise in the horizontal plane; the sagittal view, however, shows an S-shaped contour. In the two other cases that we have studied the curves closely resemble those shown in the figures.

These examples of the pathway of the consecutive electrical axes in cases of atrial flutter show an individual variation which is not surprising. Any circus movement which is present in such cases might be expected to vary from patient to patient. The axes rotate in a manner compatible with a circus, and in each instance return to the initial direction.

Atrial Fibrillation.—We have analyzed tracings taken in three planes from six patients with atrial fibrillation. Because of the variation from moment to moment of the record of atrial activity, it is obvious that tracings obtained in the three planes, unless taken simultaneously with three instruments, must be tracings that cannot be properly combined into a three-dimensional figure. The curves plotted from the directions of the consecutive atrial axes of some sections often showed beautiful circular contours; curves derived from other segments of the same record might be extremely irregular and bizarre. In some instances one plane might show repeated circles, differing in size and

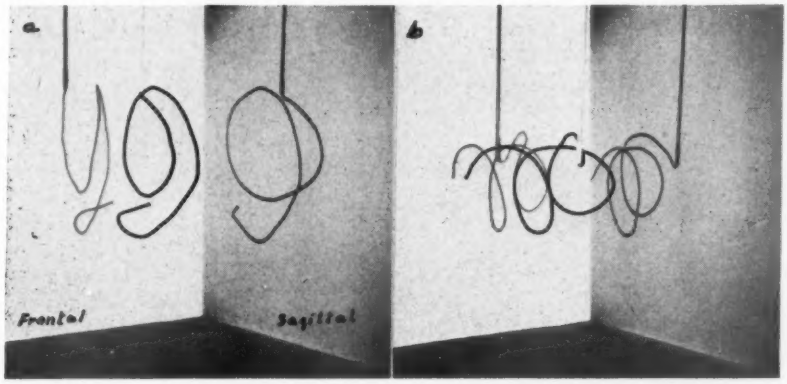

Fig. 2.—*a* and *b*, Atrial fibrillation in two cases of mitral stenosis.

shape, while the other planes failed to show this. Fig. 2, *a*, illustrates this possibility. We have combined the tracings in the sagittal and frontal planes from a patient with mitral stenosis, realizing, of course, that these are not simultaneous tracings in the two planes, but are records of two entirely different impulses, taken at different times. The sagittal shadow shows a variable circus, whereas the frontal shadow is much more irregular and further removed from a circus. Thus an irregular circus movement in the atria may yield projections upon the three planes of recording which show good agreement with, or great deviation from, a circus, depending on the plane in which the electrical forces are recorded, or in which the model is viewed. The same point is borne out by Fig. 2, *b*, constructed from the records of another patient with rheumatic mitral stenosis.

Paroxysmal Tachycardia.—The data just depicted show that this procedure is capable of revealing the serial change in the direction of the

momentary electrical axes, at least with the base lines employed, which appears, in agreement with Lewis, to be compatible with the presence of a circus movement in cases of atrial flutter and fibrillation, although of course it does not prove its presence. It now remains to ascertain, by analogous methods, the nature of these curves in paroxysmal tachycardia.

CASE 1.—J. P., a white man, aged 67 years, John Sealy Hospital No. 56427, was admitted Dec. 20, 1943. For the preceding four years he had had cardiac asthma; for six months before admission there had been frequent attacks of paroxysmal nocturnal dyspnea. Orthopnea, dependent edema, and oliguria had been present for eight days. The blood pressure was 120/80; numerous asthmatic râles were heard over the entire chest; hepatomegaly, ascites, and marked edema of the legs were noted. The venous pressure was 27 cm. of saline. Twenty-four grains of digitalis leaf were given in the first forty-eight hours. On Dec. 21, 1943, 2 c.c. of mercupurin were injected intravenously, causing a urinary output of 6,100 cubic centimeters. On December 22, the electrocardiogram showed paroxysmal atrial tachycardia, with partial A-V block; the atrial rate varied from 154 to 200 per minute. At 4:30 that afternoon atrial flutter was present (Fig. 1, *c*). Tachycardia had recurred the next morning, December 23; during the day 13 grains of quinidine were given, and, on December 24, sinus rhythm was present. The tachycardia recurred on December 27; quinidine failed to interrupt the disturbance, and the patient died December 30.

The electrocardiographic data on this patient are summarized in Fig. 3, showing those obtained during the paroxysmal tachycardia on December 23, and contrasting them with those of the sinus rhythm on December 24. These data include, in order from above downwards, a strip from a limb lead; strips from Leads I and III in each plane of the chest leads; the curve of the momentary electrical axes calculated for each 0.01 second; and, lastly, a photograph of a three-dimensional model combining the curves for the three planes, and showing the frontal and sagittal projections. The photographs show, more clearly than a description, the difference in direction and contour between the course of the consecutive atrial axes during tachycardia and during sinus rhythm.

CASE 2.—M. M., a white woman, aged 34 years, John Sealy Hospital No. 10902, was admitted Aug. 24, 1943. Rheumatic mitral stenosis had been recognized in 1929, and the diastolic murmur of aortic insufficiency had first appeared in 1940. In spite of frequent periods of complete rest in bed, in the preceding three years she had maintained compensation with difficulty, although she had taken a daily ration of digitalis leaf. During this time she had shown atrial flutter and fibrillation, both of which had been controlled by the use of quinidine. At the time of this admission she manifested the usual signs and symptoms of congestive heart failure. On August 25 sinus rhythm was recorded; on August 27 there was a paroxysm of atrial tachycardia which was terminated by carotid sinus pressure. On September 9 and 10 atrial fibrillation was present; this was replaced spontaneously by tachycardia with 2:1 A-V block on September 12. Quinidine in a dose of 0.6 Gm. was given, and, on September 13, sinus rhythm was found. On September 14, however, flutter was present. From September 25

through October 4, tachycardia with 2:1 A-V block was present, with the atrial rate at about 200 per minute. This was not controlled by repeated administration of quinidine; additional digitalis, however, given October 6 to 8, converted the mechanism into atrial fibrillation, which was, in turn, converted to sinus rhythm by 2.3 Gm. of quinidine on October 11. Tachycardia recurred October 14; again it was not stopped by quinidine, but was converted on October 28 to sinus rhythm by digitalis. Quinidine in a dose of 0.3 Gm. three times daily maintained the sinus rhythm.

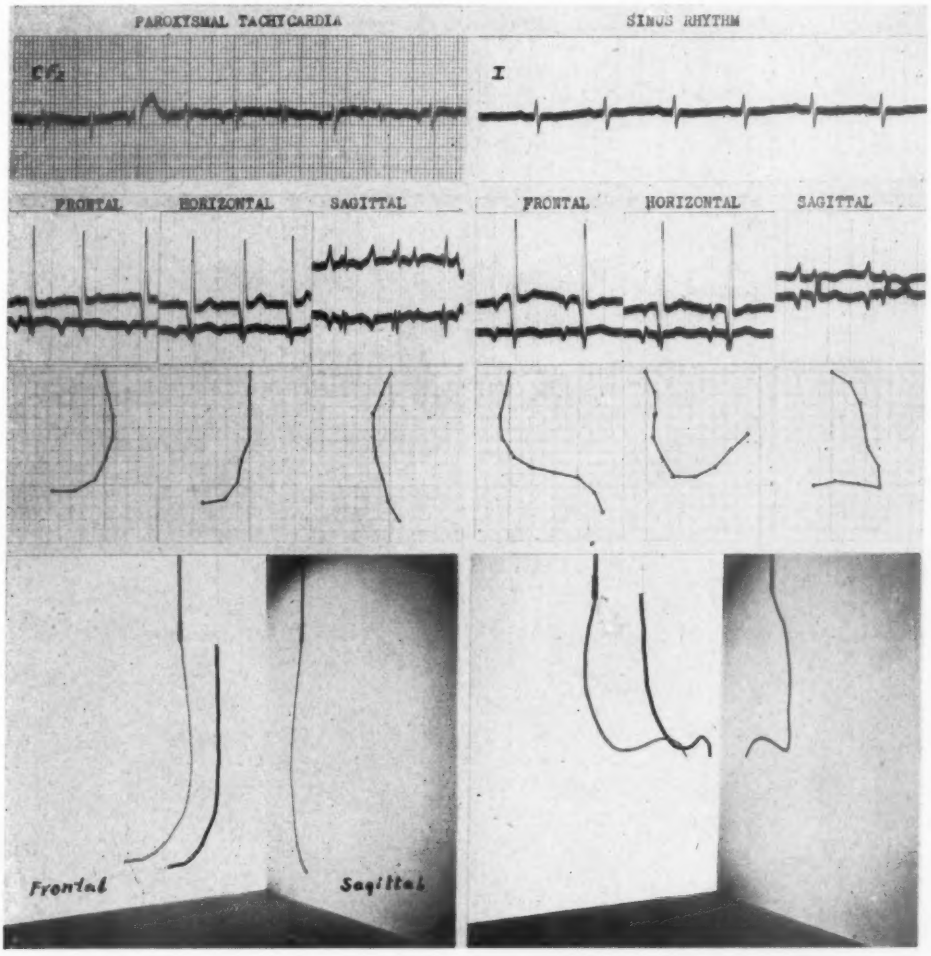

Fig. 3.—Paroxysmal tachycardia compared with sinus rhythm in Case 1. The upper electrocardiograms show the mechanism. The second line contains short pieces from the three planes, as indicated, of Leads I and III, recorded simultaneously. Below them are the consecutive axes for each 0.01 second. The photographs are of models constructed in the manner described in the preceding paper.

Fig. 4, *a*, shows a strip of Leads I and III, taken simultaneously in the frontal plane; below is a model representing the course of the consecutive atrial axes during the attacks of atrial tachycardia. Fig. 4, *b*, gives the same data for a period of sinus rhythm.

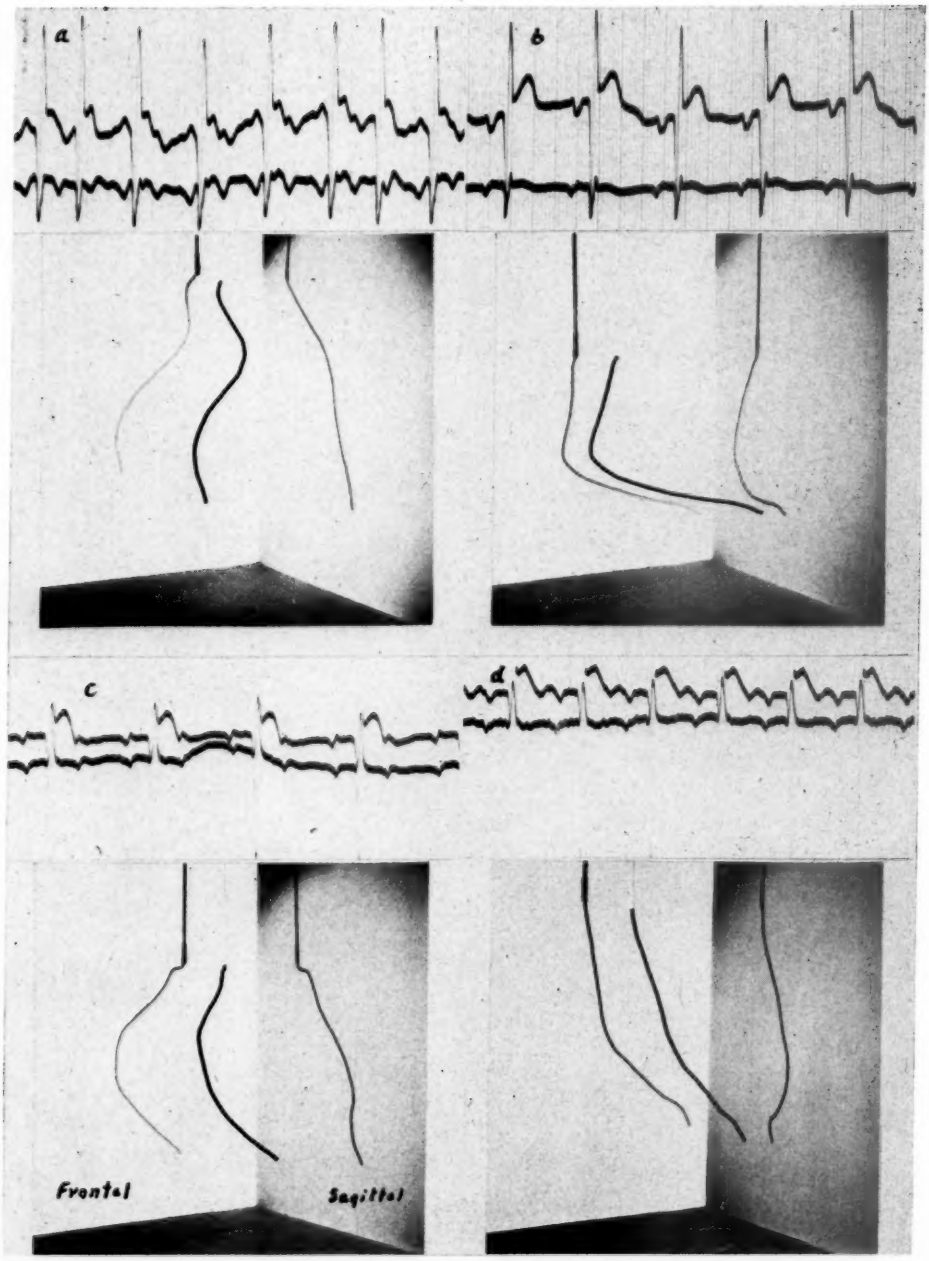

Fig. 4.—*a*, Leads I and III in the frontal plane, and below the model representing the atrial axes, during paroxysmal tachycardia in Case 2. *b*, Same, during sinus rhythm. *c*, Case 3 during paroxysmal tachycardia; see text for position of the electrodes. *d*, Case 3 with sinus rhythm.

CASE 3.—A. S., a white man, aged 59 years, John Sealy Hospital No. 79775, was first admitted on Jan. 26, 1943. During the ensuing nine months he had three other admissions, and died Oct. 9, 1943. The blood pressure varied little from 200/120; renal insufficiency was present, with chronic uremia. A pericardial friction rub was heard three weeks before death. On Sept. 8, 1943, frequent atrial premature beats were recorded. On September 15 and 16 paroxysmal atrial tachycardia, with 2:1 A-V block, was present; this stopped spontaneously, and subsequent tracings showed sinus rhythm. Necropsy showed a greatly enlarged heart (1,000 grams), fibrinous pericarditis, and marked renal arteriolosclerosis.

Fig. 4, *c* and *d*, compares the tracings in the frontal plane and the atrial axes during tachycardia and sinus rhythm. The tracing in Fig. 4, *c*, was taken with the right arm electrode at the right nipple and the left arm electrode on the left nipple. The triangle thus formed in the frontal plane must be viewed from the back, but, for the model below, correction has been made to conform with the routine positions. The curve in Fig. 4, *d*, was taken with the electrodes properly placed.

CASE 4.—M. J., a Negro woman, aged 62 years, John Sealy Hospital No. 62324, was admitted Jan. 18, 1944. She had been in the hospital in 1939 and 1941, both times with congestive heart failure caused by hypertensive heart disease. Before this admission her physician had given her digitalis leaf in a dose of 0.1 Gm. three times daily for nine days. This had caused some decrease in the edema, but had also caused nausea, vomiting, and diarrhea. Her first electrocardiogram showed atrial tachycardia; the rate varied from 140 to 158 per minute, with aberration and alternation of the QRS complexes, and occasional A-V block with dropped beats. Carotid sinus pressure increased the grade of A-V block. Quinidine was given, and appeared to be responsible for reversion to sinus rhythm on January 21. Although clinically she seemed to be improving, she died suddenly January 23. Necropsy showed cardiac enlargement (680 grams), aortic and coronary arteriosclerosis, renal arteriolosclerosis, and chronic passive congestion.

Fig. 5, *a*, shows the tracing in the frontal plane, and the model derived as previously described, during the tachycardia; Fig. 5, *b*, is from data obtained during sinus rhythm.

CASE 5.—G. H., a Negro woman, aged 53 years, John Sealy Hospital No. 84222, was admitted Nov. 23, 1943. Three weeks before admission she had fainted; a physician found that she had arterial hypertension, and prescribed digitalis tablets, of which she took sixteen in the following week. At that time she saw another physician, who gave her 0.6 Gm. of digitalis three times daily for three days. The exact amount of digitalis that she had taken was not definitely ascertained, but it was obviously too much; this clearly warranted the diagnosis of digitalis intoxication and adequately explained the severe nausea and vomiting which were present on admission. The blood pressure was 170/94; there was no evidence of congestive heart failure. The electrocardiogram on November 24 showed atrial tachycardia; the rate was 125 per minute, with partial A-V block of the Wenckebach type. On November 26, 2:1 A-V block was present. By November 29 sinus rhythm had appeared spontaneously.

From a clinical standpoint this patient was thought to have paroxysmal atrial tachycardia with A-V block of the type which we have observed to result from digitalis overdosage. The P waves in the

limb leads showed slight differences during the tachycardia with block, when compared to those recorded later. Fig. 5, *c* and *d*, shows the frontal plane electrocardiograms and the three-dimensional models for the tachycardia and the sinus rhythm. Although not as marked as those in the other cases, the differences appear definite, and are, we believe, enough to support the clinical conclusion that the tachycardia was probably of ectopic origin.

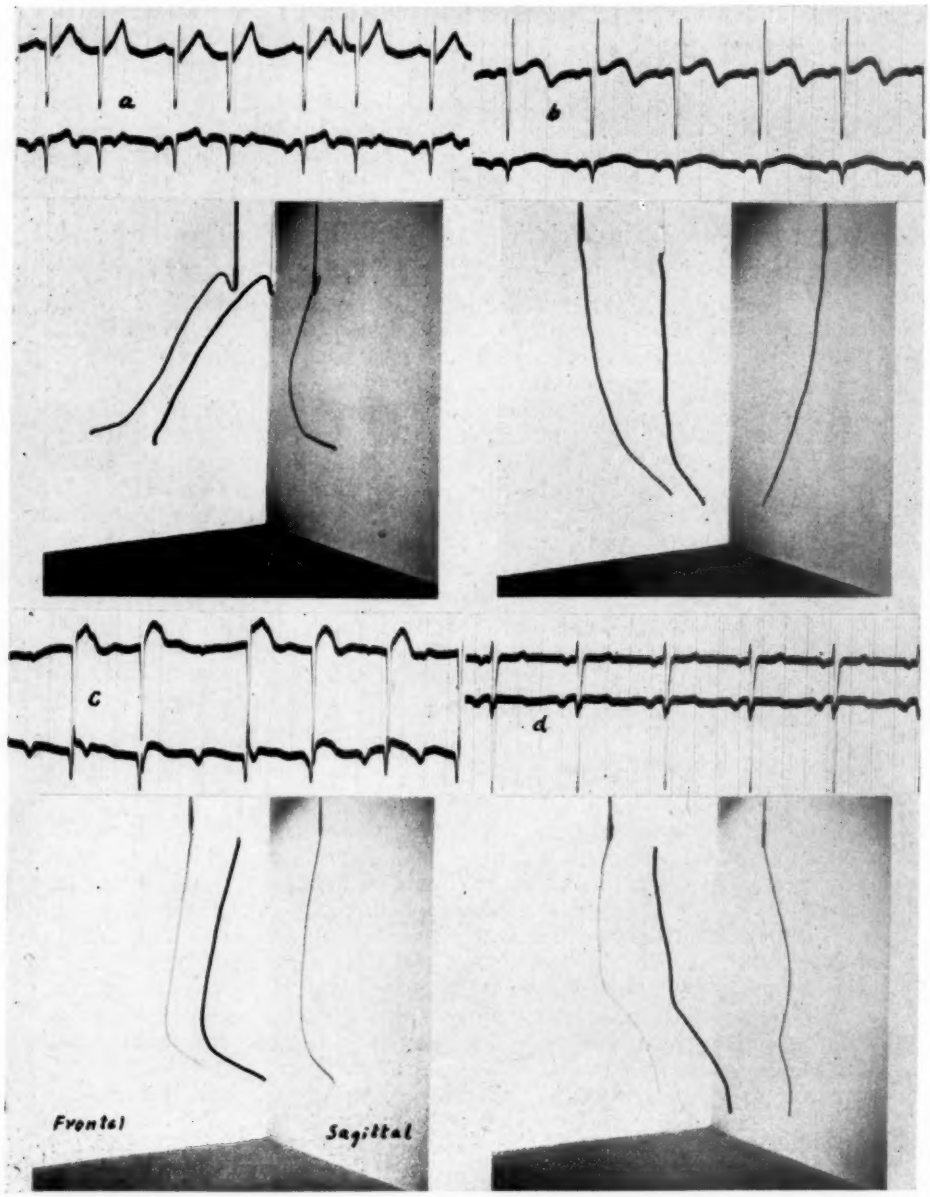

Fig. 5.—Leads I and III from the frontal plane, with model below. *a*, Case 4 during paroxysm, and *b*, during sinus rhythm. *c*, Case 5 during paroxysm, and *d*, during sinus rhythm.

CASE 6.—O. J., a Negro man, aged 50 years, John Sealy Hospital No. 83208, was admitted Sept. 8, 1943, with congestive heart failure. He had had bronchial asthma since childhood. The exact anatomic cardiac diagnosis was uncertain. The abnormalities on examination included pulmonary emphysema; a basal diastolic murmur, loudest in the second left intercostal space; and roentgenologic evidence of en-

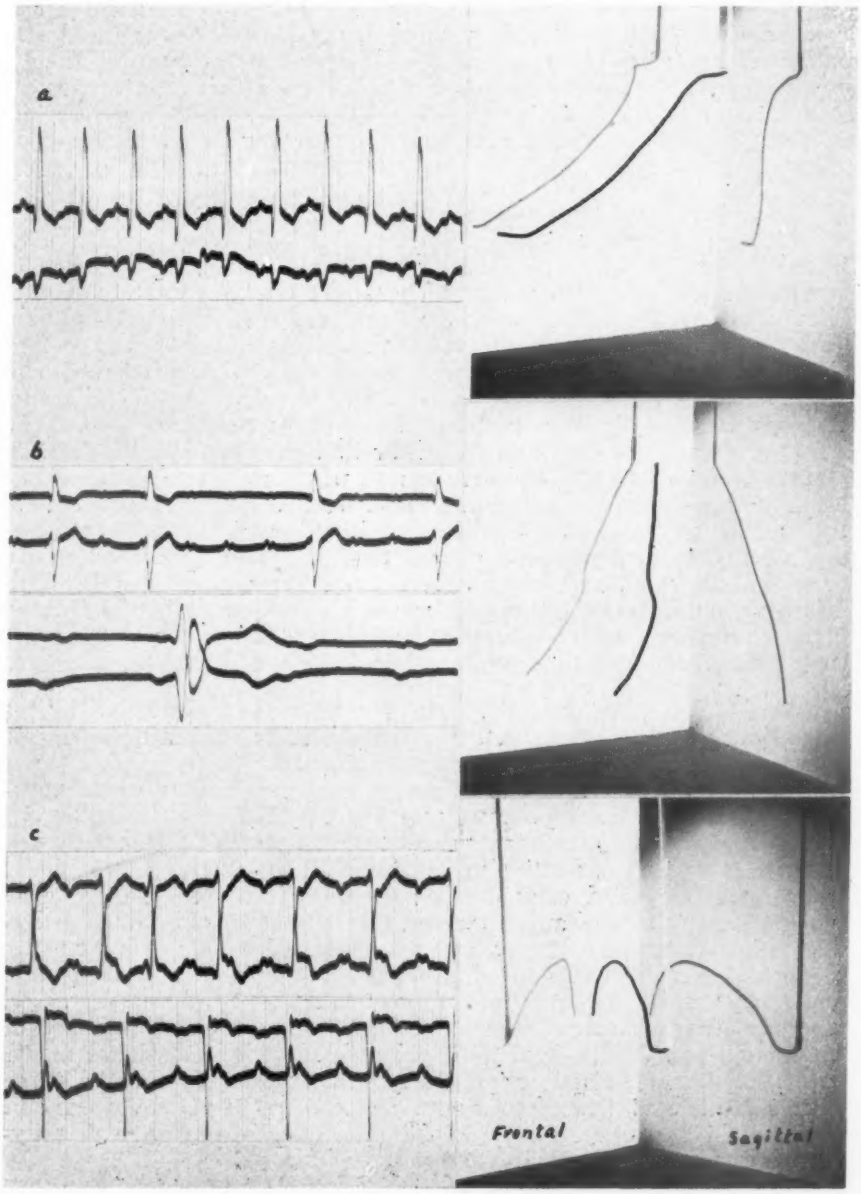

Fig. 6.—Axes during paroxysmal tachycardia. *a*, Leads I and III in the frontal plane, with the model of the atrial axes in Case 6. *b*, Case 7; limb Leads I and III above, with frontal plane Leads I and III at film speed of 75 mm. per second, below. Model on right. *c*, Case 8; Leads I and III of sagittal plane above, and frontal plane below, with photograph of model.

largement of the pulmonary conus and the right atrium and ventricle. The electrocardiogram showed right axis deviation and evidence of right ventricular strain. Some observers felt that they could detect the diastolic rumble of mitral stenosis. Digitalis leaf was given in 0.3 Gm. doses for two days, and 0.1 Gm. daily thereafter; a satisfactory loss of edema resulted. On Oct. 16, 1943, paroxysmal tachycardia developed, with an atrial rate of 139 per minute. Three hours later the rate was 146 per minute, and for the following two days stayed at about 150 per minute. Fig. 6, *a*, shows the tracing of Leads I and III in the frontal plane, obtained at the slower rate; fortunately, the P waves may be clearly distinguished at this time, although later curves at the faster rate did not permit this. The patient left the hospital October 21, and no record during sinus rhythm was obtained. He died suddenly at home Nov. 21, 1943.

CASE 7.—P. H., a Negro man, aged 79 years, Out-patient Department No. 44908, had paroxysmal tachycardia with A-V block on Aug. 24, 1943. He had been under observation and treatment for hypertensive heart disease since 1930. After an absence of two years he visited the Clinic Aug. 17, 1943, with marked congestive heart failure. Digitalis leaf in a dose of 0.3 Gm. daily was advised. He returned August 24; on this day the electrocardiogram showed atrial tachycardia with a rate averaging 166 per minute, usually with 2:1 A-V block; the grade of block was greatly increased by carotid sinus pressure. Fig. 6, *b*, shows a strip of Leads I and III in the limb leads and in the frontal plane. This patient was the first one on whom we recorded the chest leads in three planes, and, as in Case 3, we had not yet standardized the position of the electrodes. Their position is such that, as in Case 3, the triangle formed must be viewed from the back. Correction has been made in the model to conform to the other curves taken in what was later found to be the proper method. The curves in the frontal plane were taken with a film speed of 75 mm. per second. This patient refused to enter the hospital, and died a few days later at home.

CASE 8.—E. M., a white man, aged 54 years, John Sealy Hospital No. 83393, was admitted Sept. 22, 1943, with a history of pain in the chest, nervousness, and weight loss, progressing during the preceding three months. There were no signs of congestive heart failure or of hyperthyroidism. The blood pressure was 110/80. The electrocardiogram showed paroxysmal atrial tachycardia, with an atrial rate of 188 per minute. The A-V conduction varied from 1:1 to 3:2 or 2:1 A-V block. Deep respiration and carotid sinus pressure increased the grade of block. The atrial mechanism was not interrupted by quinidine or digitalis administration. The patient was relieved of his symptoms by digitalization, which produced a fairly constant block with a slow ventricular rate. He died suddenly at home Nov. 24, 1943. Fig. 6, *c*, shows a strip of Leads I and III, taken in the sagittal and frontal planes on Oct. 26, 1943. Beside them is a three-dimensional model constructed from the data obtained from the curves for the three planes. This curve is exceptional in that, instead of passing down and to the right, as has been usual in the other cases of paroxysmal tachycardia, it curves up, backward, and to the left.

The characteristic feature of the curves derived during flutter and fibrillation is that the axes return to their initial direction, with cyclic repetition. In contrast, the curves obtained during paroxysmal tachy-

cardia are, in general, like those obtained in sinus rhythm; most of them pass down and to the right, usually forward, occasionally backward; in one instance the curve moved up, backward, and to the left. In no instance was there any tendency for the curves to return to their original direction.

DISCUSSION

For the reasons that we have previously cited, we had anticipated that the curves derived during paroxysmal tachycardia would resemble those in flutter or fibrillation. Since we have failed to demonstrate this similarity, it seems necessary to consider carefully two possibilities, namely, (1) that the evidence which seems to support the likelihood of a circus movement may be viewed in such a light that it is compatible also with the existence instead of an ectopic pacemaker, and (2) that a circus movement may still pass through one of the nodes, but that only that portion involving the atrial muscle is perceptible electrocardiographically.

The limb leads do not give a strictly frontal plane projection, and the axes for the frontal plane cannot be approximated from the limb leads. This is probably because of the fact, which Schellong[11] has pointed out, that the arms and legs are not attached to the body at points in a plane, but are rather connected through large surfaces. Hence the electrical forces measured by the limb leads are derived not from the frontal plane alone, but from all the planes parallel to the frontal, and consequently are influenced by the projection on the sagittal, as well as the frontal, plane. For this reason the electrical axes apparent in the limb leads do not coincide with those of a planar projection, and conclusions based on that assumption are open to question. The axes estimated from the limb leads in the above cases were straight down, or slightly to the left and down, in five of the eight cases. In the other three the axes pointed up and to the left. In one of these, Case 8, the axis from the limb leads agreed roughly with part of the frontal plane projection of the three-dimensional momentary axis. This was the only instance of such agreement.

Of this small group of patients with paroxysmal tachycardia, seven fell into the type with A-V block which we have previously discussed.[1] They further bear out the conclusions previously drawn, namely, that myocardial disease and digitalis medication are important factors predisposing to this disturbance of cardiac mechanism. They show the marked irregularity of atrial rate also previously noted. We may note again the alternation of the P-P cycle length, with prolongation of the blocked cycle. We have attributed this to reflex vagal inhibition of the ectopic site of impulse formation, in a manner analogous to that which has been carefully analyzed by Ashman and Gouaux[12] in a patient with complete heart block.

Vagal stimulation increases the degree of A-V block in flutter and fibrillation, and may slightly increase the atrial rate; in paroxysmal

tachycardia, the vagus may cause A-V block or increase its degree, and may slow or stop the paroxysm. Barker, et al., have attributed the slowing and frequent interruption of atrial tachycardia which results from reflex vagal stimulation to depression of conduction of a circus movement as it passes through nodal tissue. This, of course, is entirely compatible with what is well known about vagal effects on A-V nodal tissue, although it does not take into account the occasional precipitation of a paroxysm by acetyl-β-methylcholine or by vagus stimulation.[13] Many cases of persistent paroxysmal tachycardia in which the A-V junctional tissue was depressed enough to produce some grade of A-V block have been reported. Of the eight cases studied above, in all except Case 6 there was A-V block. There is, unfortunately, a dearth of information about the action of the vagus, or of drugs, upon the rate of stimulus formation in the atrial muscle, but it seems reasonable to suppose that vagal stimulation may inhibit rhythmicity in an ectopic focus in a fashion similar to its effect commonly observed clinically on the rhythmicity of the S-A node, A-V node, and intervening tissues. This is borne out by the study of isolated atrial muscle strips made recently by Hiatt and Garrey,[14] which showed definite depression by acetylcholine of impulse initiation in the muscle.

The effects of the vagus on conduction in the atrial muscle probably do not need to be considered as bearing on this question. Vagal stimulation is without effect on atrial conduction at ordinary rates; it does, however, facilitate conduction by reducing the refractory period of the atrial muscle when this has been prolonged by such factors as cold, compression, fatigue, anoxemia, or rates above 300 per minute.[15] The higher atrial rates of flutter and fibrillation would lead us to expect a vagal facilitation of conduction through the pathways of the atrial muscle. When overdigitalization is a factor in producing the tachycardia, the refractory period will have been shortened by the drug.[16]

The contradictory implications of the occasional precipitation of paroxysms by digitalis, acetyl-β-methylcholine, and vagus stimulation, on the one hand, and by atropine, epinephrine, or vagus disease, degeneration, or inhibition, on the other hand,[17] cannot be explained in the light of our present knowledge of atrial muscle physiology.

Both quinidine and digitalis slow or stop paroxysmal tachycardia; both delay conduction in the A-V nodal tissue. Quinidine exerts this effect on conduction in the atrial muscle by raising the threshold to stimulation, according to Wedd, Blair, and Gosselin;[18] it also diminishes the rhythmicity of muscle strips.[19] Wedd, Blair, and Dwyer[20] have also shown that digitalis slows the rate of impulse formation, without change in threshold, in atrial muscle strips. Hence the effects of both of these drugs on paroxysmal tachycardia are compatible with their having acted upon an ectopic focus. The action of digitalis upon atrial muscle, or upon foci in the muscle, is not sufficiently clear to

explain why digitalis should be the not infrequent cause of paroxysmal tachycardia, at least of the variety associated with A-V block. Its action upon the A-V conduction tissue is much better understood,[21] but none of its known effects at this point can explain why it causes paroxysms.

It might seem possible for paroxysmal tachycardia to be caused by a circus movement which passed through only a small part of the atrium, with the major portion of its pathway in the ramifications of the A-V junctional tissue, which may be very extensive, according to Kung and Mobitz[22] and Danielopolu and Proca.[23] These tissues are known to be most susceptible to those influences which depress conduction.[24] The persistence of such a circus in the presence of A-V block would require the assumption of selective block involving the fibers forming the A-V connection, but without block in the higher fibers. Nearly all tracings of paroxysmal tachycardia show some prolongation of the A-V conduction time. Occasionally, one with an unusually slow atrial rate will not; on the other hand, block as high as 6:1 has been recorded without interruption of the paroxysm.[1] Under these circumstances it does not seem justifiable to assume that a circus mechanism passes unhindered, at a rapid rate, through these highly susceptible tissues.

The S-A node is less easily subjected to study than is the A-V node, and there is far less information available about conduction through it. Lewis[25] has regarded this general area as part of the pathway of the circus movement which he has postulated as the cause of atrial flutter; his actual measurements in experimental flutter[25] included the "S-A nodal region," and showed no delay at this point in the passage of the impulse along its circular pathway. If the circus movement postulated for paroxysmal tachycardia includes an area comparable to Lewis' "S-A nodal region," it should be as readily demonstrable by our method as was the circus mechanism of atrial flutter in man by Lewis. This, of course, does not entirely exclude the possibility that the pathway includes nodal tissue whose electrical activity is presumably not measurable.

The data presented above are intended to put these questions to the test. Those presented in connection with atrial flutter and fibrillation are no different fundamentally from those of Lewis, although we have pictured them somewhat differently. They appear to support the idea that a circus movement may be present in these disturbances, although they offer no conclusive proof on this point. We have employed them merely for the purpose of showing what a presumed circus movement looks like when studied by this method. The characteristic feature of these figures is that, after a variable course, the axes return finally to their initial direction, and repeatedly inscribe a pathway which continues to conform to the general contour of a circus pathway. Those

made during flutter, also, in each instance, exhibit a hiatus opposite to a long, relatively straight limb; the latter may perhaps correspond to that time during which Lewis found little change in the direction of the axis, and which he could not satisfactorily trace in the actual pathway of the experimental cases, namely, the time when the impulse was passing posteriorly along the area of the entrance of the great veins into the atria.

As a distinct contrast, we have presented[7] the curves illustrating the momentary shifts in the atrial electrical axes in persons with normal sinus rhythm, both normal and abnormal with respect to the position or size of the atria, or to the status of the atrial musculature. These curves often show large curvature, but fail to show any tendency to point finally in their original direction.

It is with these two large groups of cases, namely, sinus rhythm and a presumed circus movement, that we wish to compare the curves obtained from patients with paroxysmal atrial tachycardia. Most of the latter group show curves which clearly resemble those obtained during sinus rhythm, with the exception of their direction, which is usually down and to the right. They resemble in some instances the curves from patients with dextroposition of the heart; in other instances, curves from patients with mitral stenosis. Those which show large curvature still fail to manifest any tendency to repeat themselves, or to point finally in their original direction; nor is the degree of curvature greater than that which sometimes occurs with sinus rhythm, e.g., Case 1 or 2 during sinus rhythm.

We must admit the possibility that a circus movement residing chiefly in the nodal tissues might not be detected by our methods; we have pointed out, however, the virtual impossibility of such a circus in the A-V node in cases of tachycardia with A-V block, a view which Barker, et al., share. A circus elsewhere probably would be easily visualized by our method, although Lewis long ago pointed out that the atrial muscle did not afford enough room for a circus movement as slow as most paroxysms of tachycardia, at accepted rates of conduction.[25] The fact that these curves in paroxysmal tachycardia show no resemblance to those found in flutter or fibrillation, but are similar to those obtained during sinus rhythm, suggests to us that paroxysmal tachycardia is probably the result of the existence of an ectopic site of impulse formation, rather than of a circus movement. These curves may be modified, as are those of sinus rhythm, by the size and position of the atria and the status of the atrial muscle as a conducting medium, as well as by the site of origin of the exciting stimulus.

SUMMARY

Curves representing the consecutive atrial electrical axes for each 0.01 second have been derived for the frontal, horizontal, and sagittal planes

from patients with atrial flutter, atrial fibrillation, and paroxysmal tachycardia, and three-dimensional models have been constructed.

The clinical experimental results of Lewis, Drury, and Iliescu have been reproduced and extended in flutter and fibrillation.

The same procedure has been applied in eight cases of paroxysmal tachycardia. The type of curve in this disturbance of atrial mechanism has been found to resemble that obtained during sinus rhythm; it differs only in direction. The characteristic features of flutter and fibrillation are not present. This fails to support the idea that a circus movement is present in paroxysmal tachycardia, and although the possibility of a circus involving the S-A node is not finally excluded, we believe that the weight of the evidence points to the existence of an ectopic site of impulse generation.

The available information on the physiology and pharmacology of the atrial musculature and nodal tissues has been reconsidered insofar as it bears on the behavior of paroxysmal tachycardia, and the view that in it an ectopic pacemaker may be operative.

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THE ANGINAL SYNDROME AS A MANIFESTATION OF HYPERACTIVITY OF THE CAROTID SINUS

MAJOR MEYER FRIEDMAN, M.C., ARMY OF THE UNITED STATES

SINCE the excellent clinical studies of Weiss and his associates,[1, 2] there have been many reports concerning hyperactivity of the carotid sinus. Many of these articles suggest that this interesting condition may be caused by, or at least be associated with, various pathologic states, such as arteriosclerotic heart disease,[3] hypertension,[4] biliary tract disease,[5] and cervical lymphadenopathy.[6] It has also been observed in cases of vegetative neurosis and digitalis intoxication.[7] In all of these conditions, the type of hyperactivity is vasovagal.

Although the diseases and drug intoxication listed above may make their presence first known by the manifestations of hyperactivity of the carotid sinus, it is also possible that the latter may in itself simulate a functional or organic disease. Thus, the carotid sinus syndrome with syncope may be confused with epilepsy, postural hypotension with collapse, the hyperventilation syndrome, or even with gastroenteritis.[8] I wish to report two cases in which the manifestations of hyperactivity of the carotid sinus simulated angina pectoris.

CASE REPORTS

CASE 1.—A medical officer, aged 35 years, was admitted to Tripler General Hospital Sept. 24, 1943. His complaint was of precordial pain beginning in the substernal area and radiating to the left hemithorax and shoulder.

The patient's past and family history was negative for cardiovascular disease.

The present illness began in February, 1943, at which time the patient began to experience sharp, pressing pain in the left hemithorax during periods of emotional tension. The pain, at the beginning, was only of several minutes' duration and seldom severe enough to be incapacitating.

On June 20, 1943, however, while carrying a heavy box a very short distance, the patient felt weak and dizzy, perspired very freely, and experienced a crushing sort of substernal pain which radiated to the left shoulder and upper part of the left arm. The pain disappeared within several minutes. Again on July 12, 1943, after a day of moderate activity, while walking on level ground and after experiencing the same symptoms as described immediately above, he fell to the ground, unconscious. A fellow medical officer, who was with him at the time of his syncope, stated that the patient's pulse could not be felt and that the skin became pale, cold, and clammy. He recovered consciousness within twenty seconds, but the pain in the chest and shoulder persisted for several more minutes. A similar attack, this time without syncope, occurred on August 9 as he was walking to his quarters, but he stopped, inhaled a pearl of amyl nitrite, and obtained immedi-

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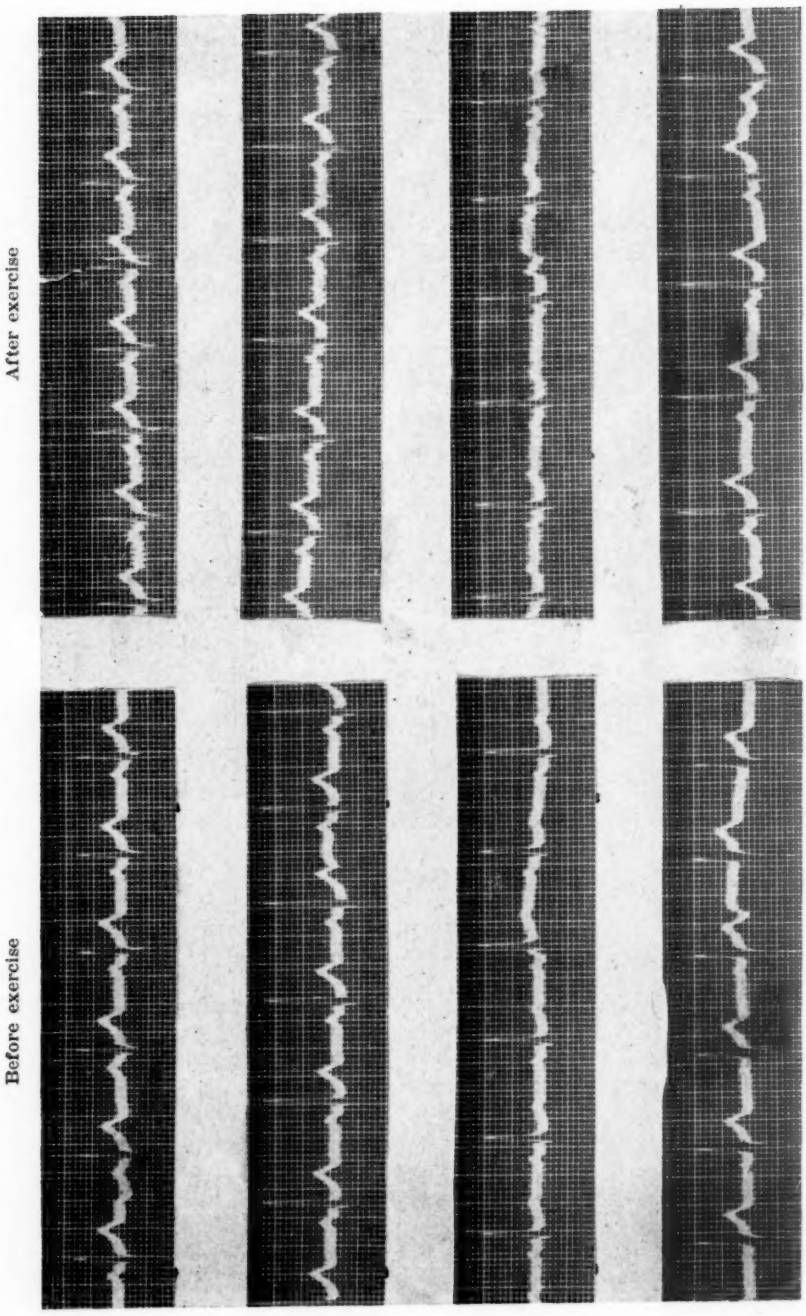

Fig. 1.—Electrocardiogram in Case 1 before and after climbing sixty steps.

ateate relief. On Aug. 21, 1943, the patient stooped over to place a golf ball upon a tee, and, while doing so, experienced extreme dizziness, weakness, and precordial pain with radiation to the shoulder and left arm. When he straightened up the symptoms immediately disappeared, and he was able to continue his game without further symptoms, despite the hilliness of the course. After this attack he had almost daily attacks of dizziness and anginal pain. He believed that he might be suffering from coronary artery disease with angina pectoris.

The patient was emphatic in declaring that exercise and exertion did not precipitate his anginal syndrome, but he admitted that sudden movements of his head frequently preceded the symptoms, although he had never before thought of the two phenomena as being related.

The patient was a well-developed person of healthy appearance. Other than dermatographia, excessive perspiration, easily produced urticaria (mechanical), and the reaction to massage of the right carotid sinus area, physical examination was negative. When massage was done, he became pale, perspired very freely, complained of dizziness and substernal pain, lost consciousness, and had several localized, clonic convulsions of the upper extremities. His blood pressure, which was 120/70 before massage, fell so low soon after the sinus was stimulated that it could not be measured. Concomitant with the fall in blood pressure, the heart rate slowed from 76 beats per minute to complete asystole soon after the onset of syncope. It was observed that the patient experienced his dizziness and precordial pain before the vasovagal effects occurred, and that syncope did not take place until the vasovagal effects became profound. The test was performed repeatedly and the same syndrome resulted almost invariably. An electrocardiogram taken during one such test showed complete asystole as the patient lost consciousness. The patient stated that the syndrome produced by carotid sinus massage was identical with that which he had had prior to his admission to the hospital.

While in the hospital, the patient went through various strenuous exercise tests (climbing stairs, running, jumping) which he did without abnormal symptoms or signs referable to his cardiovascular system. Electrocardiograms (Fig. 1) were taken before and immediately after the performance of very strenuous exercise. Both were normal and quite similar to each other. The basal metabolic rate was normal, and roentgenologic studies of the heart, urinalysis, examination of the blood, and serologic reactions showed nothing abnormal.

The patient was transferred to another hospital for further definitive treatment.

CASE 2.—A 21-year-old soldier was admitted to Tripler General Hospital Oct. 10, 1943. His complaint was of precordial pain beginning just lateral to the sternum and radiating to the left shoulder and left arm.

The patient's past and family history was negative for evidence of cardiovascular disease.

His illness began in 1937, at which time, while dancing, he suddenly became dizzy and was seized by a dull but intense pain in the left hemithorax which radiated to the left shoulder and arm. He immediately ceased dancing and the pain disappeared within several minutes. Thereafter he continued to have these attacks of dizziness and precordial pain, and, immediately prior to his hospital admission, he was having them every two or three days. He had observed that, although exercise did

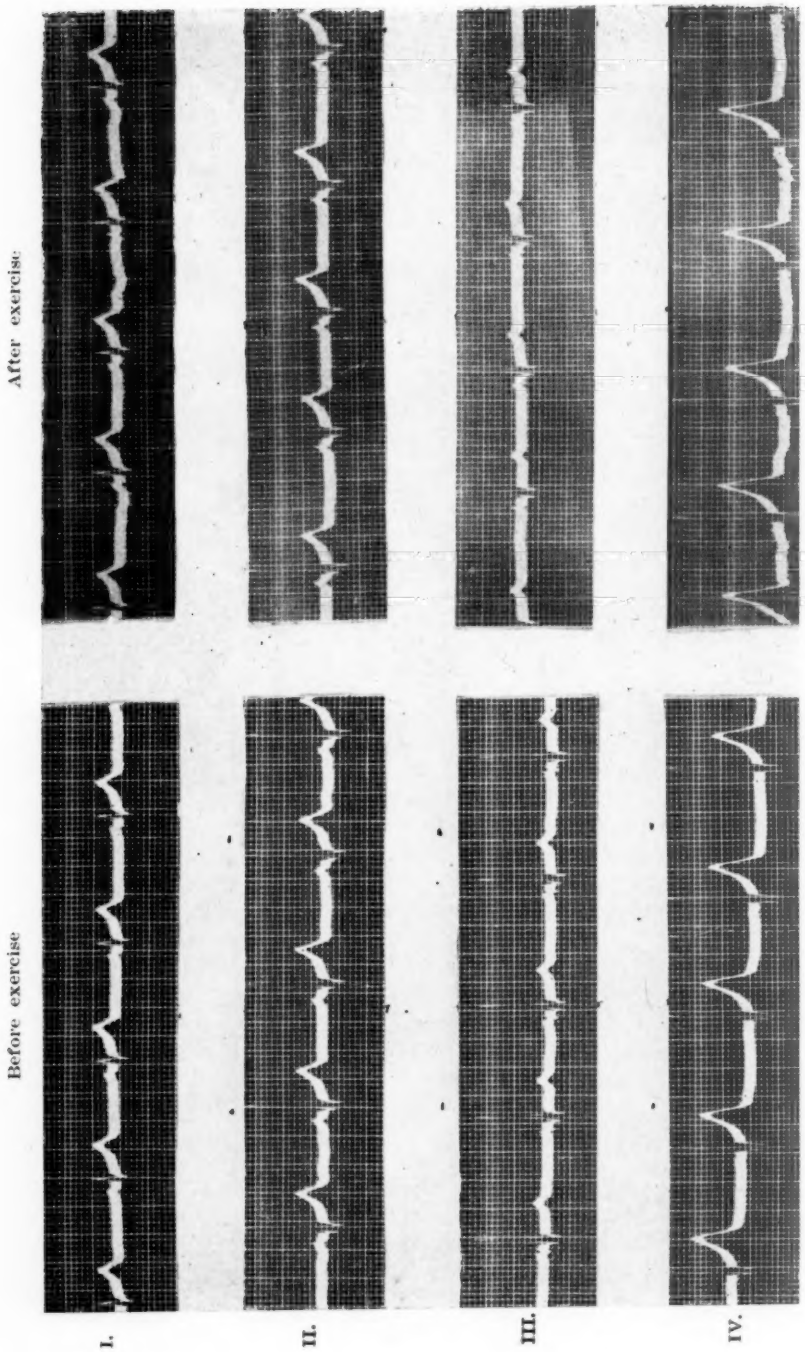

Fig. 2.—Electrocardiogram in Case 2 before and after climbing sixty steps.

not induce an attack, sudden movements of his head might easily provoke one. Consequently, he made it a point to turn his head slowly and not to bend over rapidly to tie his shoe laces; otherwise, he would become dizzy and have the anginal pain. He fainted several times on such occasions, but always recovered consciousness within ten to fifteen seconds and had no apparent sequelae. On admission, the patient was convinced that he had serious heart disease.

The patient was poorly developed; his state of nutrition was fair, but he exhibited signs of profound anxiety. The remainder of the physical examination was completely negative except that the right carotid sinus was hypersensitive. When the latter was massaged with the patient in the sitting position, he began to complain of dizziness and anginal pain identical with that which he experienced before admission to the hospital. When the massage was continued, the patient lapsed into syncope. Unlike Case 1, however, no significant vasovagal effects followed massage, either before, during, or after syncope. Thus, the heart rate and blood pressure were 80 per minute and 110/80, respectively, before sinus massage, and, as he became unconscious, the heart rate and blood pressure were 74 per minute and 120/75, respectively, with little change during syncope or immediately afterwards. The test was repeated many times and the same syndrome invariably occurred. One milligram of atropine, administered parenterally, did not prevent induction of the syndrome.

This patient, also, was made to take various exercise tests (climbing steps, running, jumping), but he never experienced dizziness, anginal pain, or any other abnormal cardiovascular symptom during or immediately after the performance of such tests. The electrocardiogram (Fig. 2) was normal both before and after exercise. The sedimentation rate and basal metabolic rate were normal. Roentgenologic studies of the heart, urinalysis, examination of the blood, and serologic reactions were negative.

The patient was transferred to another hospital for further treatment.

DISCUSSION

The occurrence of precordial pain, dyspnea, and collapse strongly suggests the possibility of coronary artery disease. It is noteworthy that one of our patients, himself a physician, believed that he might be suffering from coronary artery disease with angina pectoris, and had taken amyl nitrite for relief. Thus, any syndrome arising from an extracardiac source which produces symptoms similar to those frequently associated with cardiac ischemia or infarct may prove difficult to differentiate from a syndrome caused by organic heart disease. This becomes understandable when one remembers that, in many cases, the diagnosis of coronary artery disease[3] may be made only by the history obtained from the patient.

In the histories of the two patients reported herein, however, certain facts were elicited which clearly indicated the essential nature of the disorder, allowing differentiation from the syndrome of angina pectoris associated with coronary artery disease. Thus, both patients emphasized the frequent occurrence of vertigo preceding the anginal pain, which is not commonly seen in patients suffering with coronary artery

disease. Both patients also denied that strenous exertion or heavy work induced attacks, although both were able to recollect that abrupt movements of the head might initiate the syndrome, an observation which in itself strongly suggests the presence of carotid sinus hypersensitivity. The frequent occurrence of syncope, with complete and instantaneous recovery, further indicated the true nature of their anginal syndrome. In coronary artery disease with angina pectoris, syncope rarely occurs unless profound changes have taken place in the heart itself—changes which will produce signs and symptoms which are not evanescent or of several minutes' duration as were those in our cases.

Besides the differentiation allowed by the facts culled from the histories of these two patients, the physical examination further clarified the diagnosis. The discovery that the carotid sinus was hypersensitive, and the reproduction of the syndrome from which they suffered prior to admission by stimulation of the sensitive sinus pointed to the true cause of the difficulty. The negative evidence for cardiovascular disease afforded by the electrocardiogram, the roentgenogram, the exercise tests, and other laboratory data further secured the diagnosis of carotid sinus syndrome.

The converse of the present syndrome has been reported by Sigler[3] to occur in cases of proved organic heart disease, namely, that hyperactivity of the carotid sinus mechanism frequently may be found in arteriosclerotic heart disease. He further describes this carotid sinus syndrome as cardio-inhibitory in nature. If this is true, the possibility of hyperactivity of the carotid sinus must be kept in mind not only as a process initiated by a diseased heart, but also as a process which in itself may simulate the symptoms arising from disease of the heart. The evaluation of any history of vertigo, anginal pain, and syncope must be doubly cautious if error is to be avoided. But if the history is not typical of coronary artery disease; if there have been attacks of vertigo and syncope; if this history is coupled with the presence of hyperactivity of the carotid sinus, which, on stimulation, reproduces the patient's symptoms (particularly with no vasovagal changes); and if there are no organic, functional, or laboratory indications of cardiovascular disease, even on severe exertion, it would be most unfair to the patient to tell him that he had organic heart disease. It would be more expedient to hold such a diagnosis in abeyance until objective signs of organic heart disease make their appearance—a phenomenon which probably will not occur in such cases.

SUMMARY

1. Two cases of carotid sinus syndrome are reported in which anginal pain, similar to that associated with cardiac ischemia, occurred as a manifestation of hyperactivity of the carotid sinus.

2. Stimulation of the hyperactive carotid sinus reproduced the anginal syndrome in both cases.

3. The differentiation of anginal pain associated with the carotid sinus syndrome from that associated with cardiac ischemia secondary to coronary artery disease is discussed.

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PHYSIOLOGIC EFFECTS OF CARBON DIOXIDE WATER BATHS ON ALVEOLAR CARBON DIOXIDE TENSION, SKIN TEMPERATURE, AND RESPIRATORY METABOLISM

WALTER S. MCCLELLAN, M.D., MILTON A. LESSLER, M.S., AND ALICE T. DOULIN
SARATOGA SPRINGS, N. Y.

INTRODUCTION

IN STUDYING the influence of carbon dioxide mineral water baths on the circulation, observations on the changes in alveolar carbon dioxide tension, skin temperature, and respiratory metabolism have been made. The results indicate that definite increases occur in the alveolar carbon dioxide tension and in the amount of carbon dioxide eliminated through the lungs when the subject is submerged in the natural carbon dioxide mineral waters. These changes do not appear when the same subject is exposed to plain water.

PROCEDURES

A. Alveolar Carbon Dioxide Tension.—A special experimental room was equipped to carry out these observations. It contained a large tub (200 gallons), into which hot or cold water, carbon dioxide mineral water, or plain water could be drawn. Over this tub a sponge-rubber-covered stretcher was suspended. The stretcher was fitted with a foot-rest, an adjustable reclining back, and a headrest, enabling the patient to rest comfortably in a semireclining position during the entire observation. A pulley arrangement made it possible for the operator to lower the stretcher and patient into the tub and take him out again without any effort or motion on the part of the patient (Fig. 1). During the entire experimental period, the patient's mouth and nose were covered with a rubber mask with an inflated edge. This was connected to a set of flutter valves by means of kink-proof tubes (as shown in Fig. 1), and allowed the patient to breathe outdoor air. The mask was removed only for the few seconds necessary to obtain the alveolar sample by means of the Henderson-Morriss tube.[1]

The experiments were conducted from 9 to 10 A.M., about one and one-half hours after the patient had had a standard breakfast. He was allowed to rest for twenty minutes with the face mask attached. During this period, the bath, either of carbon dioxide or plain water, was drawn at 35° C. (95° F.). The carbon dioxide baths were prepared with the natural mineral water from the Lincoln Springs in the manner used in regular mineral water baths at The Saratoga Spa. They contained a supersaturation of 30 to 34 per cent carbon dioxide by volume.

From the Medical Department of The Saratoga Spa, Saratoga Springs, N. Y.
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After the rest period, when pulse and respiration had reached a constant level, the base alveolar sample was taken. The patient was lowered into a 35° C. mineral water or plain water bath, and alveolar samples were taken at the fourth, eighth, twelfth, and sixteenth minutes. Then the patient was raised from the bath, dried, covered, and allowed to rest (still attached to the mask). Alveolar samples were taken ten and twenty minutes after the bath. The same procedure was used in the bath series with the patient breathing room air except that the inhale valve of the mask was not attached to the outdoor air inlet. This allowed the patient to breathe the air above the tub.

The samples of room air, outdoor air, and alveolar air were collected in mercury-evacuated Bailey sampling bottles.[2] All samples were analyzed for carbon dioxide in duplicate in a Haldane-Boothby-Sandiford gas analysis apparatus, with an accuracy of ± .01 per cent, and duplicate analyses had to check within these limits. Complete analyses of outdoor

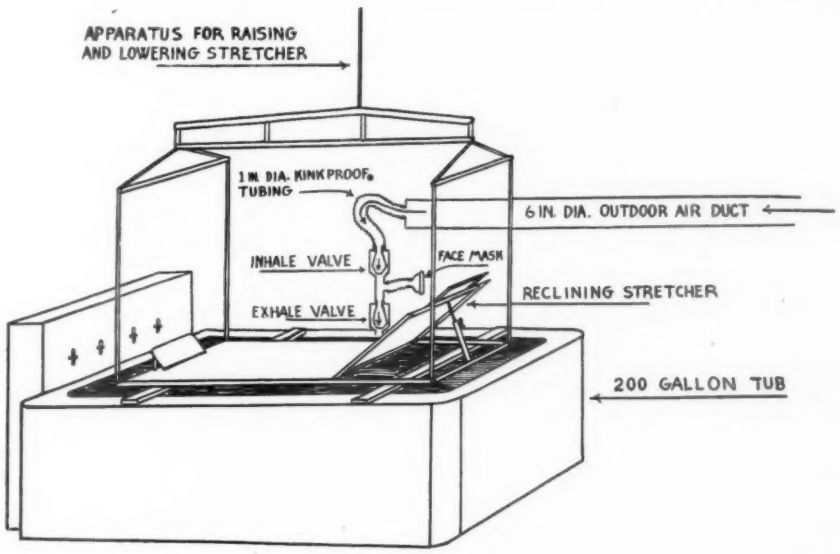

Fig. 1.—Plan of experimental setup. The experimental tub has pipe connections for both hot and cold, plain and mineral, water. The stretcher is suspended over the tub with a mechanical device for lowering and raising the stretcher and patient into and out of the bath without any effort on the part of the patient. It shows the air connections from outside to the mask, so that the patient may breathe outside air during the entire observation.

air were made from time to time to check on the accuracy of the machine and to make sure that the patient was breathing air with .03 to .04 per cent carbon dioxide. The room temperature was recorded, and ranged from 25° C. to 30° C., but did not vary more than 0.5° C. during any experimental period. Barometric readings were taken, and the carbon dioxide tensions were calculated by means of the formula:[1]

$$P_{CO_2} = \frac{C}{100} \times (B - W)$$

P_{CO_2} = Carbon dioxide pressure in millimeters of mercury at 38° C.
C = Percentage of carbon dioxide in alveolar sample
B = Recorded barometric pressure in millimeters of mercury
W = Pressure in millimeters of mercury of water at 38° C.

TABLE I

TYPICAL PROTOCOL

EXPERIMENT 9		
TIME (A.M.)	PROCEDURE	TOTAL NUMBER OF MINUTES
7:30	Standard Breakfast Tomato juice 2 slices of buttered toast 1 cup of coffee with cream and sugar	
8:30 to 9:07	Rest period on cot in experimental room	37
9:08	Patient transfers from cot to stretcher suspended over tub	
9:10	Mask attached over nose and mouth of patient	5
9:12	Carbon dioxide mineral bath drawn	8
9:15	Washing out of dead space in Tissot machine	3
9:18	Tissot emptied and spirometer set at zero	1
9:19 9:24	Base run started Base run ended	5
9:24 to 9:26	Gas volume and temperature reading of base run	2
9:26	Stretcher with patient lowered into a 35° C. mineral water bath containing 34 per cent supersaturation of carbon dioxide by volume	
9:26 to 9:29	Two one-minute washouts of machine	3
9:30 9:35	Second test started (Procedure same as base run) Second test ended	5
9:35 to 9:37	Gas volume and temperature reading	2
9:37	Two one-minute washouts of machine (Procedures same as base run)	3
9:40 9:45	Third test started (Procedure same as base run) Third test completed	5
9:45	Stretcher and patient raised out of the tub. Patient dried with towels without rubbing, and covered with a warm sheet and light blanket. Ten-minute rest with mask still attached	10
9:55	Two one-minute washouts of machine	3
9:59 10:04	Fourth and last test started Last test completed	5

B. Skin Temperatures.—For the study of changes in skin temperature, observations were made at four different temperature levels, namely, 29.4° C. (85° F.), 32.2° C. (90° F.), 35° C. (95° F.), and 37.8° C. (100° F.). No changes occurred in the bath temperatures during the periods of observation. The baths were given from 9 to 10 A.M., after the patient had had a standard breakfast. Two series of baths were made at each temperature level, on each subject, usually on successive days. On the starting day of a series the plain water bath was given first, followed by the carbon dioxide water bath, and, on the next day, the order of the baths was reversed. Eighty bath series were given to six men who were physically normal. The patient was im-

TABLE II

PERSONAL DATA—EXPERIMENTAL SUBJECTS

NUMBER	NAME	SEX	AGE (YR.)	WEIGHT (LB.)
1	W. C.	M	64	172
2	C. E.	M	50	180
3	W. M.	M	46	175
4	A. D.	M	43	215
5	C. G.	M	19	155
6	R. V.	M	45	136
7	D. B.	F	25	125
8	J. C.	M	29	137
9	T. A.	M	40	156
10	G. D.	M	37	133
11	H. F.	F	36	200
12	E. D.	M	29	130
13	Q. C.	M	22	128
14	L. P.	M	25	140
15	J. S.	M	18	128

mersed to shoulder level in a carbon dioxide or plain water bath at the given temperature. Each minute he put either his right or left foot on a small platform fastened to the side of the tub, and the toe and instep were immediately blotted dry with absorbent paper. Skin temperature readings (using the Taylor dermatherm) were taken of each foot on alternating minutes during the sixteen-minute bath. The thermocouple was applied to the great toe and instep of each foot, and both readings were completed within fifteen seconds. Between the baths, the patient reclined on a couch in the experimental room. The room temperature was recorded, and ranged from 27° C. to 35° C., but did not vary more than 1° C. during any experimental period. These observations were made during June, July, and August, which accounts for the occasionally high room temperatures in the series.

C. Respiratory Metabolism.—For the study of the respiratory metabolism a Tissot spirometer was used to collect the expired air of patients for four separate periods. The first, or base period sample, was taken with the patient resting on the stretcher over the tub, the second and third period collections were made with the patient in the bath, and the fourth period sample was taken ten to fifteen minutes after the patient was removed from the bath but while he was still resting on the stretcher. Expired air was collected in a Tissot spirometer for the study of respiratory metabolism, as described by Bailey.[2] Samples of the expired air were analyzed in a Haldane-Boothby-Sandiford machine according to the procedures outlined by Boothby and Sandiford.[3] Table I gives a protocol of the experimental procedure. This procedure was uniform for all the bathing experiments.

Four types of observations were made. In order to accustom the subject to the procedure, all of the steps in Table I were followed in a preliminary observation, except that no bath was drawn in the experimental tub. The data obtained covered a training period for the subject, and were used for additional check on other controls. In all instances at least two experimental observations were made, one in which the natural carbonated mineral water was used in the bath, and a second when plain water at the same temperature was used. In three cases repeated series of observations were made, so that a total of ten comparable sets of data were obtained. In addition, two subjects were

studied in a bath of plain water to which 5 pounds of sodium chloride and 5 pounds of sodium bicarbonate were added in order to simulate the mineral content of the natural mineral water without the carbon dioxide.

The personal data regarding the fifteen subjects used in these studies are presented in Table II. Reference to individual observations will be made by the numbers indicated in this table.

EXPERIMENTAL DATA

A. *Alveolar Carbon Dioxide Tension.*—A series of tests were carried out to ascertain the concentration of carbon dioxide gas in the air above the tub. The averages of these data are presented in Tables III and IV.

We found by measurement that the patient's nose and mouth were about 3 inches above the top of the tub, and four experiments were made to ascertain the effect of time on the carbon dioxide gas concentration above the bath at this level.

These data made it evident that the patient must breathe outdoor air in order to study carbon dioxide absorption from the bath. This was accomplished by attaching the patient to the mask and valves as already described (Fig. 1). Analyses of the air that the patient was breathing while attached to this setup never showed more than 0.04 per cent carbon dioxide, and agreed with Carpenter's[4] observations as to the constancy of the outdoor air.

Sixty-two experimental baths at 35° C. were given to seven different male subjects. Two men had less than 85 per cent of normal vital capacity, but showed the same type of results as those subjects with normal vital capacity. These two showed greater variability in results than the other subjects.

Since only one experimental run was made each day, differences in the physiologic state of the subject were indicated by variations of alveolar carbon dioxide tension at the end of the initial rest period.

TABLE III

35° C.—CARBON DIOXIDE WATER BATH*—WITH AND WITHOUT PATIENT

	TOP OF TUB	3 INCHES ABOVE TOP	6 INCHES ABOVE TOP	12 INCHES ABOVE TOP
No patient	4.28†	.54	.55	.55
Patient in tub	----	2.26	1.84	1.82

*Samples were taken as soon as bath was drawn.
†Percentage of carbon dioxide.

TABLE IV

35° C.—CARBON DIOXIDE WATER BATH*—PATIENT IN TUB

	START	3 MIN.	6 MIN.	9 MIN.	12 MIN.	16 MIN.
Patient in tub	2.44†	1.34	1.01	.65	.68	.56

*Average of samples taken at height of patient's nose.
†Percentage of carbon dioxide.

However, the general direction of each set of observations was determined by the experimental procedure used, and was not dependent on the level of the resting alveolar tension. To check this, two experiments were made in which the patient took no bath, but went through all the movements and samplings used in the regular procedure. The average results of these two tests, as presented in Table V, indicate the small amount of variation inherent in the technique.

TABLE V

	AFTER 20-MINUTE REST PERIOD	4 MINUTES IN TUB, NO WATER	8 MINUTES IN TUB, NO WATER	12 MINUTES IN TUB, NO WATER	16 MINUTES IN TUB, NO WATER	10 MINUTES OUT OF TUB	20 MINUTES OUT OF TUB
P_{CO_2} mm. Hg at 38° C., dry	43.0	42.4	42.2	42.2	42.0	42.8	43.0

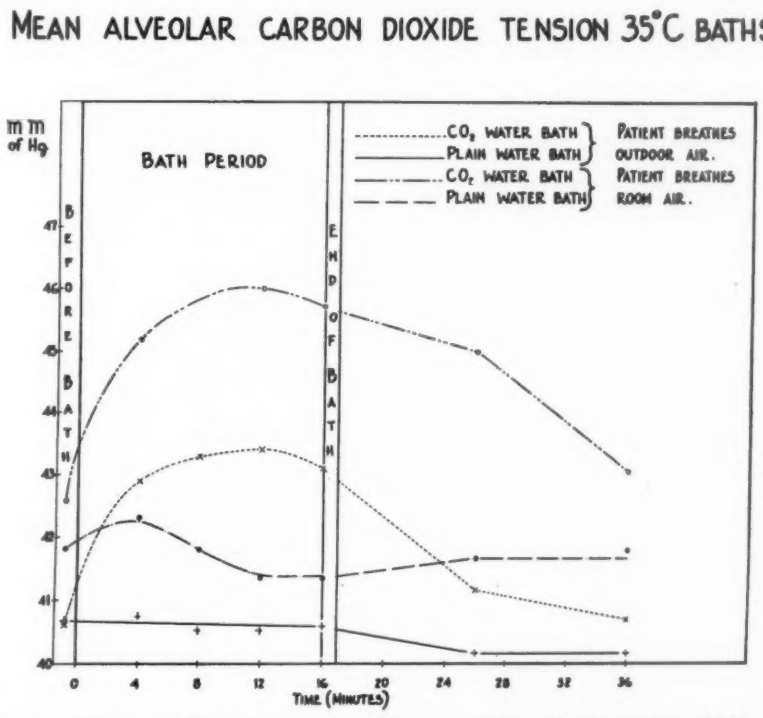

Fig. 2.—The curves show the levels of alveolar carbon dioxide tension during the base period before the bath, with subsequent changes in and after both the mineral and the plain water baths. Observations were made as indicated when the patient breathed outside air (———— and - - - - - - - -) and when he breathed the air over the tub (—.— and—. .—).

The carbon dioxide concentration in the alveolar air is presented as tension in millimeters of mercury at 38° C., dry. The mean results of the four different experimental procedures are shown in Table VI, and are presented graphically in Fig. 2.

B. *Skin Temperature.*—Skin temperature observations on the great toe and instep were made at each reading, but no significant differ-

TABLE VI

MEAN ALVEOLAR CARBON DIOXIDE TENSION IN 35° C. BATHS

	CO_2 WATER— PATIENT BREATHES OUTDOOR AIR	PLAIN WATER— PATIENT BREATHES OUTDOOR AIR	CO_2 WATER— PATIENT BREATHES ROOM AIR	PLAIN WATER— PATIENT BREATHES ROOM AIR
Base alveolar tension after 20-minute rest	40.6*	40.7	42.6	41.9
4 minutes in bath	42.9	40.7	45.2	42.3
8 minutes in bath	43.3	40.5	45.7	41.8
12 minutes in bath	43.4	40.5	46.0	41.4
16 minutes in bath	43.1	40.6	45.7	41.4
10 minutes after bath	41.2	40.2	45.0	41.7
20 minutes after bath	40.7	40.2	43.1	41.8
Maximum rise above base	2.8	0.0	3.4	0.4
Percentage rise above base	6.9	0.0	8.0	0.9

*P_{CO_2} = millimeters of mercury at 38° C., dry.

ences were noted between the two curves. The starting skin temperatures of the instep were 0.5° C. to 1° C. higher than those of the toe, but during the baths they approached the same level. For the sake of brevity, only the skin temperatures of the great toe are included.

Series 1, consisting of plain and carbon dioxide mineral water baths at 29.4° C., showed no marked differences in skin temperatures between the carbon dioxide water, and plain water, baths. The skin temperature dropped to a level 0.5 to 1° C. above the bath temperature. Series 2, at 32.2° C., showed nearly the same results as Series 1, but there was a tendency for the skin temperature to be higher in the carbon dioxide water baths. In both these series, the patients felt slightly chilly while in the tub. In Series 1 the skin temperatures were above the bath temperature, and, in Series 2, 3, and 4, the skin temperatures were below the bath temperature.

Series 3, at 35° C., and Series 4, at 37.8° C., showed consistently higher skin temperatures in the carbon dioxide baths. The readings were 0.5 to 1° C. higher at the end of the carbon dioxide water bath. This difference was noted in the skin temperatures of all the patients, and therefore it is considered of some significance. In the baths at 35° C. (Series 3), the skin temperature rose to a point 1.5 to 2° C. below the bath temperature, and then leveled off. In the baths at 37.8° C. (Series 4), the nearest approach was 2.5 to 3° C. below the bath temperature. Typical results of each bath series are shown in Fig. 3.

The order in which the baths were given had no measurable effect on the results. Series in which the plain water bath was given before the carbon dioxide water bath showed almost the same curves as when the reverse order was used. All the subjects had a distinct hyperemia of the skin when they emerged from the carbon dioxide water baths. The hyperemia was confined to the area of the body covered by the carbon dioxide water, with a distinct line of demarkation between the

immersed and unimmersed skin areas. This was not present when the patient emerged from the plain water bath.

C. *Respiratory Quotient.*—The material assembled from these studies on seven subjects is presented as mean averages in Table VII. Data covering the amount of carbon dioxide eliminated and of oxygen consumed, the respiratory quotient, and the respiratory minute volume during the mineral and the plain water baths are presented.

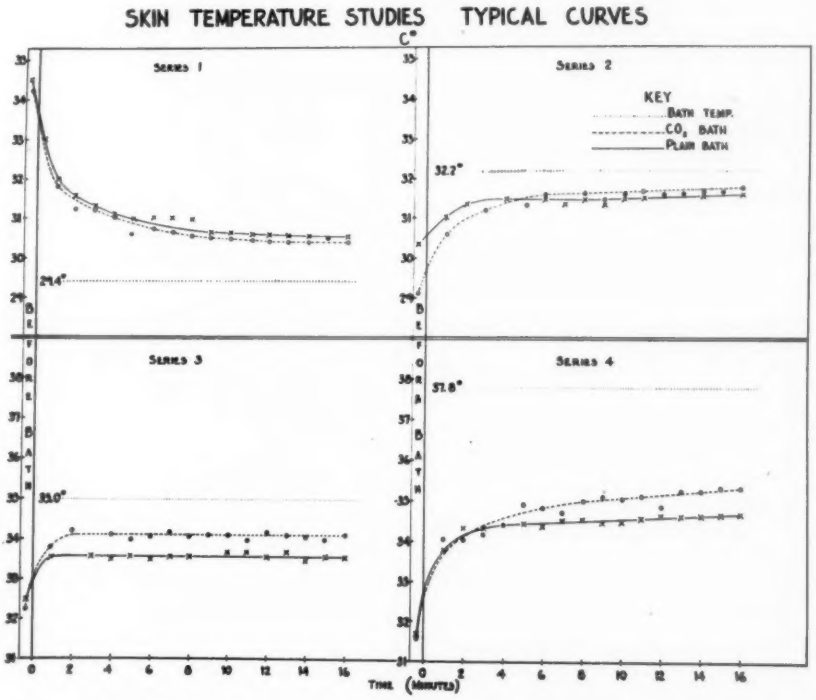

Fig. 3.—The curves are drawn from data plotted to represent the average of the observed temperatures. The starting temperature is influenced by the room temperature, which is recorded in the table. In all observations the temperature shifted toward the temperature of the bath, and, within two to four minutes, reached a relatively constant level except in the carbon dioxide bath at 37.8° C., where the curve continued to rise slowly during the entire observation.

In order to show the individual results in the seven subjects studied, the actual variations obtained in periods two, three, and four, as compared to the base period in each of the experimental observations, have been calculated and are presented in Fig. 4. The variations in these data which were greater than the base period are represented by columns extending upwards from the base, or zero, line. The variations which represent a decrease in the findings are indicated by columns extending downward from the base line.

Carbon dioxide: It will be seen from a study of Fig. 4 that striking changes occurred in the carbon dioxide elimination during the two periods in the mineral water bath. In all observations there was an

TABLE VII

RESPIRATORY DATA*

PERIOD	CARBON DIOXIDE ELIMINATED (C.C./MIN.)	OXYGEN ABSORBED (C.C./MIN.)	RESPIRATORY QUOTIENT	MINUTE VOLUME LITERS
Mineral				
Base run	190.6	194.0	0.98	6.03
In bath	226.4	194.5	1.16	6.71
In bath	236.3	187.9	1.26	7.01
After bath	192.9	195.9	0.99	6.06
Plain				
Base run	190.7	197.1	0.97	6.04
In bath	186.6	190.8	0.98	5.73
In bath	186.5	193.3	0.97	5.77
After bath	187.8	195.9	0.96	5.88

*Each figure in the table represents the mean average of the ten comparable observations on the seven subjects studied.

increase which varied from a minimum of 22 to a maximum of 68 c.c. per minute. In the period following the bath the variations showed an equal number of increases and decreases.

The carbon dioxide elimination which occurred during the plain water bath was entirely different; in the large majority of observations there was a slight decrease which was not considered of real significance. Also, in the period after the bath the elimination of carbon dioxide was at the same level as during and before the bath in plain water.

Oxygen consumption: The oxygen consumption during these observations showed no consistent variation from the base period in either the mineral or plain water baths. The number of observations showing decreases practically equalled the number in which increases occurred. In either case, the variation from the base period was not considered significant.

Respiratory quotient: From the data obtained for the carbon dioxide elimination and the oxygen consumption during these studies it follows that a marked increase in the respiratory quotient would occur. During the periods in the carbon dioxide baths this change was noted, as indicated in Fig. 4. Respiratory quotients as high as 1.3 were obtained in some cases.

The quotients for the base periods cannot be considered basal because all observations were made following a light, standard breakfast. This breakfast was largely carbohydrate, and, therefore, many quotients were above the usual basal level. The type of mask which could be obtained for these observations had only a single outlet. This increased slightly the usual dead space, not sufficiently to produce discomfort, but apparently enough to cause slight variations in obtaining exact figures for the actual amount of oxygen consumed. This experimental factor was recognized, but it is not felt that it materially influenced the variations which occurred when comparable observations were made on the different subjects.

Minute volume: A definite increase in the minute volume output of the subjects during the carbon dioxide bath was noted. It occurred in all but one observation. The variations reported in the figure showed a wider range of increase than was found in the carbon dioxide eliminated. The variations in the minute volume during the plain water baths, for the most part, showed some decrease from the base period.

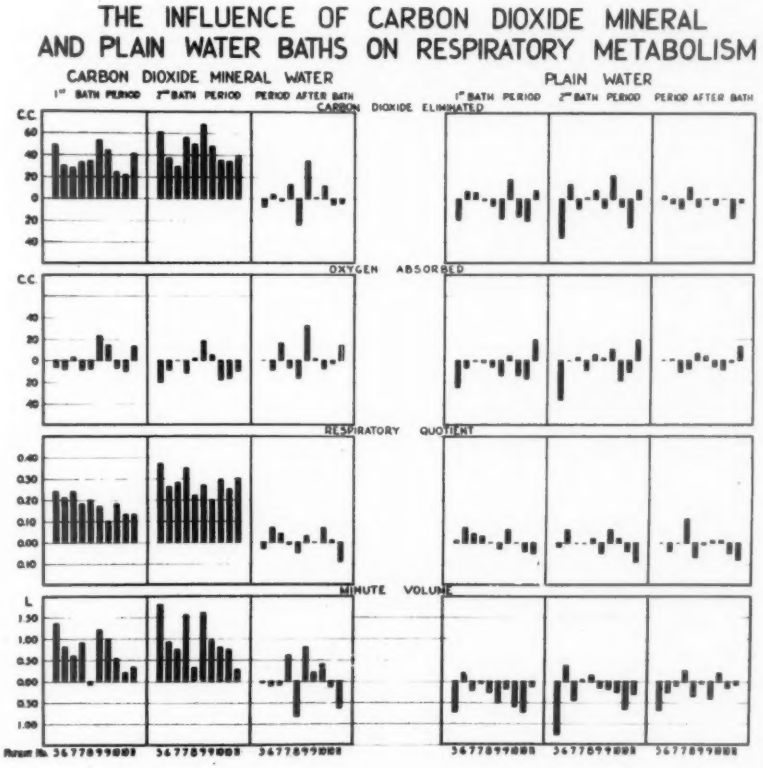

Fig. 4.—Each column represents the actual variation from the base period data of carbon dioxide, oxygen, respiratory quotient, and minute volume obtained during the periods in and after the bath. Columns extending upward from the zero line indicate increases, and those downward show decreases.

Artificial saline baths: In order to check the influence of the saline constituents in the mineral water baths without the carbon dioxide, two subjects were tested in plain water baths to which were added sodium chloride and sodium bicarbonate in amounts similar to those present in the mineral water. In this bath the subjects were exposed to all of the effects of the mineral water except the carbon dioxide. The metabolic data obtained from these two experiments showed no appreciable variation from those obtained from the same subjects in the plain water bath. Table VIII presents actual data of the analysis of the water used in this prepared bath, with a comparison to similar data obtained on the natural mineral water from the Lincoln Springs.

TABLE VIII

ANALYSES NATURAL MINERAL WATER AND ARTIFICAL SALINE WATER

	DATE	CHLORINITY (MG./LITER)	ALKALINITY (MG./LITER)
Lincoln water (natural mineral)	12/2/42	1835	2295
Artificial saline water	12/2/42	2260	2115
Artificial saline water	1/5/43	2180	2055

DISCUSSION

There has been much speculation and experimentation relating to the interchange of carbon dioxide through the skin. Hediger,[5] in a series of carefully controlled experiments, showed that carbon dioxide dissolved in water could pass through the skin. Chambers with a side opening containing water with different concentrations of carbon dioxide were sealed against the skin. The carbon dioxide diffused out of those chambers which contained more than 4 volumes per cent, and those with less than this amount took up carbon dioxide until the concentration reached 3.8 volumes per cent. Cobet and Häbler,[6] Groedel and Wachter,[7] and Harpuder,[8] using other experimental methods, confirmed Hediger's observations. Their work showed that changes occur in the respiration and blood picture when patients are given carbon dioxide baths which could best be explained by the passage of carbon dioxide through the skin. Recent studies by Stein and Weinstein[9] showed that significant and prolonged elevation of the skin temperatures of patients resulted from using artificial carbon dioxide baths on the lower extremities. They also demonstrated capillary dilatation by means of a capillary microscope with a photographic recording apparatus. In this study, they found that both the arterial and venous limbs of the capillaries were larger, and that the blood flow was greater when the limb was exposed to the water containing carbon dioxide. They considered that these observations supported the idea that dilatation of the smaller vessels occurred, and that the increase of blood flow recorded by their plethysmographic studies suggested that this dilatation may have occurred also in the larger vessels of the extremities.

A. *Alveolar Carbon Dioxide Tension.*—Certain changes in the blood picture can be studied by means of alveolar air sampling, as pointed out by Carpenter and Lee[10] and Cournand, Baldwin, et al.[11] Cournand and Richards[12] state that the carbon dioxide tension in the blood of normal persons tends to remain at a constant level. Carpenter and Lee[10] found that, with a trained subject, the alveolar carbon dioxide, taken at fifteen-minute periods on two different days, showed the results given in Table IX.

It was necessary to know the variation inherent in the technique to ascertain whether or not the observed changes were significant. The actual variation in the alveolar CO_2 tension in the control experiments

TABLE IX

DATE	NUMBER OF DETERMINATIONS	AVERAGE ALVEOLAR CO_2 PER CENT	AVERAGE ALVEOLAR CO_2 TENSION (P_{CO_2})
May 7	20	5.97 ± 0.11	42.4*± 0.7
May 16	25	5.98 ± 0.12	41.9 ± 0.8

*Approximate (calculated from Carpenter's data, assuming temperature at 38° C. and pressure at 760 mm.)

(Table V) was only 1 mm. of mercury. The changes that occurred in plain water baths varied only slightly from that figure, but the alveolar carbon dioxide tension in the carbon dioxide water baths ranges from 2.1 to 6.3 mm. of mercury, a rise of 5 to 10 per cent above the resting level. The changes observed in carbon dioxide baths are produced by some factor which is not present in the plain water baths.

The small changes in alveolar carbon dioxide tension during the plain water baths are probably caused by the general relaxing effect of 35° baths and changes in breathing due to the pressure of the water. When the patient is lowered into the tub there is a slight shock because of the difference between the skin temperature and the water temperature, but this is soon compensated for by the adjustment of the body mechanisms. However, when the patient is placed in a carbon dioxide bath, besides these minor adjustments, there is a distinct rise in the alveolar carbon dioxide tension. This rise can be measured while the patient is in the carbon dioxide water bath, and is evident for some time after the patient leaves the bath.

A comparison of the height of the mean curves of the alveolar carbon dioxide tension during carbon dioxide water baths shows the effect of the carbon dioxide in the air of the room (Table VI and Fig. 2). The patients, when breathing room air, showed a 1 per cent greater alveolar carbon dioxide change, and the return to resting alveolar tension was delayed. When the patient was breathing outdoor air, there was a tendency to return to the resting alveolar carbon dioxide tension soon after the bath (Fig. 1).

Carpenter and Lee[10] state: "It has frequently been shown that the carbon dioxide tension of the arterial blood and the carbon dioxide tension of the alveolar air run parallel in normal subjects and are nearly identical." Thus, the rise in alveolar carbon dioxide tension found in these studies indicates a rise also in the arterial carbon dioxide tension. Therefore, the absorption of carbon dioxide from the baths, which increases the arterial carbon dioxide tension, may explain some of the beneficial effects noted in patients with cardiac and vascular conditions after they have taken this type of treatment.

B. *Skin Temperature.*—The studies of skin temperature reported here were made to ascertain whether or not significant changes occur in the carbon dioxide bath, which, if present, would indicate dilatation of peripheral vessels. As a control, the subjects were always observed in a plain water bath at the same temperature as that used for the

carbon dioxide bath. A reversal of the order of giving the baths was made in every series; therefore, the subject acted as his own control, and the changes observed appear to be the result of the carbon dioxide baths. Definite, visible hyperemia of the skin was noted over the immersed area of the patients when they emerged from the carbon dioxide baths. It was not present when the subject emerged from the plain water bath.

Eighty baths were given to six normal subjects. Although their ages ranged from 18 to 46 years, much the same results were obtained in duplicate sets of experiments on each patient. Certain patients showed greater skin temperature changes than others, but all followed the same general curves. As noted in Fig. 3, the skin temperature showed considerable variations before entering the bath. These variations may have been due to differences in room temperature (27 to 34° C.), or to the general physiologic state of the patient on different days. However, these differences were eliminated within two minutes after the subject entered the bath, and the differences observed after that period are considered as a result of the influence of the baths.

The subjects were observed at four different temperature levels, and the variations noted were more evident when the bath temperature was near body temperature. The observations in a cool bath at 29.4° C. and 32.2° C. showed that the temperature of the water, rather than the action of carbon dioxide, apparently exerted the principal influence. The curves approached similar levels and did not show significant differences between the two types of baths at these temperatures.

The tendency of the skin temperature to adjust to the temperature of the surrounding medium was also evident in the warmer baths at 35° C. and 37.8° C. Here, however, the skin temperature rose to a higher level with the subject in a bath of carbon dioxide water than it did when plain water was used. The differences noted were not striking, but, when taken with the other data obtained, they point to the correctness of the idea presented by Harpuder[8] and others, namely, that carbon dioxide is absorbed through the skin and produces an effect by direct influence on the capillary network.

C. *Respiratory Metabolism.*—In considering the data presented in this section it is important to analyze certain features to ascertain whether or not the observations indicate that carbon dioxide is absorbed from the bath through the skin. The experimental data show without question that, during the exposure of the body to a mineral water bath containing large quantities of carbon dioxide in both free and combined form, there is a definite increase in the amount of carbon dioxide eliminated through the lungs without a corresponding increase in oxygen consumption. This combination results, of course, in a marked elevation in the calculated respiratory quotient. There was also an increase in the respiratory minute volume, but this was considerably less constant than the increase in elimination of carbon dioxide.

Four possible sources of the excess in carbon dioxide elimination during the periods when the patient was in the mineral water bath may be considered:

1. Increase in the oxidative metabolism throughout the body. The fact that there was no increase in the oxygen consumption during the periods in the mineral bath would rule out this possible source.

2. Release of carbon dioxide in the body. There is no evidence to show that the exposure of the body to a bath of this type produces any marked shift in the constituents in the blood other than carbon dioxide. It is well known that an increase of fixed acids in the circulating blood will result in an increase of ventilation, with the elimination of excess amounts of carbon dioxide. The fact that the subjects within a short time after the bath showed an essentially normal amount of carbon dioxide elimination is certainly evidence against a possibility of any marked change in the acid-base equilibrium of the blood.

3. Hyperventilation. One must consider carefully whether the increase in respiratory minute volume is a possible cause of the excess elimination of carbon dioxide, or whether it is the result of a stimulation of the respiratory center by circulating blood which has acquired an additional amount of carbon dioxide from some outside source. It is well known that voluntary hyperventilation may result in the elimination of excess amounts of carbon dioxide.

Data obtained during the course of these observations showed that one subject increased the minute volume by 18 per cent in one period and over 50 per cent in another by voluntary forced breathing, which resulted in the elimination of approximately 25 to 28 per cent more carbon dioxide. This was associated with relatively little change in oxygen consumption. The respiratory effort required to carry on the forced ventilation resulted, in one period, in an increase of 8 per cent in the amount of oxygen absorbed. However, the percentage concentration of carbon dioxide in the expired air fell from 3.29 to 2.52 per cent. In all observations made with subjects in the mineral water the increased ventilation was accompanied by an actual increase in the concentration of carbon dioxide in the expired air.

A review of the data presented shows that an increase in the respiratory volume occurred only during the periods when the patient was in the mineral water bath. The increase in the carbon dioxide tension of the alveolar air when the subjects were in the carbon dioxide bath indicates also an increase of carbon dioxide in the arterial blood. Since the expired air during voluntary hyperventilation has a lowered concentration or percentage of carbon dioxide, and since an increased concentration was found uniformly in these studies, it appears that the increased minute volume is the result of a stimulation of the respiratory center by the circulating carbon dioxide, rather than the primary cause of the increased carbon dioxide elimination.

4. Absorption of carbon dioxide through the skin. It is considered that this was actually the source of the excess carbon dioxide which was eliminated during the bath periods in the mineral water. In the course of a bath in this water there is a marked accumulation of carbon dioxide on the skin. The experimental observations of Hediger,[5] described above, indicate that carbon dioxide can pass through the skin.

These observations conform closely with those of Groedel and Wachter,[7] who made extensive studies of this question with the natural mineral water of Bad Nauheim, in Germany. The only difference between our data and those reported by these authors is that the increase in carbon dioxide elimination was not evident in the period of fifteen to thirty minutes after the carbon dioxide bath. Groedel and Wachter, on the other hand, found that the increase in elimination of carbon dioxide persisted from one to one and one-half hours after the bath. In our series, the changes in the amount of carbon dioxide eliminated, the rise in the respiratory quotient, and the increase of respiratory minute volume were all essentially of the same proportions as in their studies.

The changes observed in the respiratory quotient, with an elevation to 1.3, indicate without question that some extraneous source of carbon dioxide was present, because, if it were all due to food or tissue oxidation, a quotient above 1 would be impossible.

It is considered, therefore, that the evidence strongly supports the idea that the carbon dioxide eliminated during a mineral water bath is actually excess carbon dioxide which is absorbed from the bath through the skin and carried to the lungs by the blood stream. This could perfectly well explain the increased respiratory minute volume, for carbon dioxide is a well-known stimulant of the respiratory center.

D. *General Considerations.*—Justification for the extensive use of mineral water baths containing carbon dioxide in the program of treating disorders of the heart and circulation has frequently been questioned by thoughtful physicians. They say that the results are entirely due to mental and psychological factors. We think that the data presented in this communication, as well as other observations on the effects of these baths, as outlined previously by one of us,[13] show that they have a distinct and definite physiologic effect. Further studies are required, of course, to demonstrate the complete details of this effect. The observations presented in this paper are a step in that program, and are considered to be strong support for the theory that the effects produced by the use of these baths depend on the absorption of carbon dioxide through the skin.

Barach and Steiner[14] state: "Constriction of the capillary bed has been produced by acute alkalosis, and carbon dioxide administration has been followed by dilatation of these vessels." In the conclusion of their paper they point out that the addition of 2 to 3 per cent of carbon dioxide to a low oxygen mixture prevented the develop-

ment of clinical and electrocardiographic signs of coronary insufficiency when patients breathed the mixture. McDowell,[15] in studies on anesthetized dogs, found that the loss of tone caused by washing out the carbon dioxide does not affect all blood vessels alike. He concluded that the normal carbon dioxide content of the blood maintains a peripheral dilatation of the minute vessels, just as it maintains a central stimulation of the vasomotor center. Wolff and Lennox,[16] in studies of the pial vessels of trepanned cats, found that a decrease in the carbon dioxide content of the blood resulted in a moderate decrease in the diameter of pial arteries, whereas an increase in the carbon dioxide was followed by a marked increase in their size, and that dilatation was more readily produced than constriction.

In these observations each subject was his own control. In the first place, the base period on the day of the experiment was used to determine any changes resulting from the baths which followed. He also acted as his own control in that the changes resulting when he took a bath in plain water were compared with results obtained when the same patient took a bath in the mineral water. In addition, a preliminary training experiment was carried out with all subjects going through all the procedures except that no water was in the tub. Further, in two instances, additional check was made by preparing a plain water bath with the addition of salts which would bring the saline content to essentially the same level as that of the mineral water. These observations, we feel, eliminate the possibility that the salts in the water cause the variations observed. When the patients breathed only outside air during the experiments, all influence of carbon dioxide in the air over the bath was eliminated. It is, therefore, concluded that the significant changes observed in these studies are primarily due to the absorption of carbon dioxide from the mineral water through the skin.

SUMMARY AND CONCLUSIONS

1. Many observations have been made on the changes which occur in the alveolar carbon dioxide tension, the skin temperature, and the respiratory metabolism of human subjects who have been submerged in baths of either carbon dioxide water or plain water.

2. The aveolar carbon dioxide tension showed a 5 to 10 per cent rise during baths in the carbon dioxide water, and returned to the resting level about twenty minutes after the bath. There was no significant change during baths in plain water.

3. A comparison of the alveolar carbon dioxide changes during the carbon dioxide baths when the patient was breathing the air above the tub and when he breathed outdoor air indicates that the higher amount of carbon dioxide in the air above the tub caused a greater alveolar change by approximately one to two per cent.

4. There was no essential difference in the skin temperature during the carbon dioxide and plain water baths when bath temperatures of

29.4° C. (85° F.) and 32.2° C. (90° F.) were used. When the baths were 35° C. (95° F.) and 37.8° C. (100° F.), the skin temperature was 0.5 to 1° C higher in the bath of carbon dioxide water.

5. A distinct hyperemia was noted over the immersed area of the skin when the patients emerged from the carbon dioxide water baths. This was noted at all the temperatures used, and was not present when the subject emerged from the plain water baths.

6. There was a marked increase in the elimination of carbon dioxide in the expired air during the time the patient was in the mineral water bath. This increase did not occur in the plain water bath.

7. No evident variation in the oxygen consumption occurred with either bath.

8. The respiratory quotient, therefore, showed a marked elevation when the patient was in the mineral water bath.

9. There was an increase in the respiratory minute volume during the mineral water bath which did not occur with the plain water bath. This increase was not as regular as that observed in the amount of carbon dioxide eliminated.

10. The possible source of the excess carbon dioxide is discussed. The evidence supports the theory that this extra carbon dioxide is obtained by absorption of the carbon dioxide in the water through the skin and its subsequent elimination through the lungs. Other possible causes of this excess elimination, such as increased metabolism, voluntary hyperventilation, and chemical changes in the blood other than in the carbon dioxide, were considered, but cannot be accepted as valid causes for the observations.

11. It is, therefore, concluded that the results obtained in the treatment of patients with carbon dioxide mineral water baths depend, in part, at least, on the absorption of carbon dioxide through the skin and its subsequent influence on the circulation and nervous system which occurs in the process of its natural elimination by way of the blood stream and the lungs.

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ELECTROCARDIOGRAMS IN WHICH THE MAIN VENTRICULAR DEFLECTIONS ARE DIRECTED DOWNWARD IN THE STANDARD LEADS

EMANUEL GOLDBERGER,* M.D., AND SIDNEY P. SCHWARTZ, M.D.
NEW YORK, N. Y.

INTRODUCTION

THERE have recently appeared several papers describing electrocardiograms in which the main deflections in the three standard leads were downward, rather than upward.[1-5] Clinically, cases of this type have been found to fall into two groups: cases of right ventricular hypertrophy or dilatation,[3] and cases of severe myocardial damage.[2] The mechanism by which this pattern is produced, however, has not been well understood.

The problem can be partially resolved by theoretical analysis based on the fact that standard lead electrocardiograms are taken according to the following convention, arbitrarily established by Einthoven.[6] In Leads I and II, an upward deflection of the waves of the electrocardiogram will occur when the right arm is more negative (or less positive) than the left arm or left leg, respectively, and vice versa. In Lead III, an upward deflection of the waves of the electrocardiogram will occur if the left arm is more negative (or less positive) than the left leg, and vice versa. Since this is so, in a normal electrocardiogram in which QRS is upward in the three standard leads, the relations of the potentials of the extremities must be as follows:

In Lead I, the right arm is more negative (or less positive) than the left arm, or RA $<$ LA.

In Lead II, the right arm is more negative (or less positive) than the left leg, or RA $<$ LL.

In Lead III, the left arm is more negative (or less positive) than the left leg, or LA $<$ LL.

Therefore, RA $<$ LA $<$ LL.

Using a similar analysis in a record in which QRS is downwardly deflected in the three standard leads, the following condition must hold:

In Lead I, the right arm must be less negative (or more positive) than the left arm, or RA $>$ LA.

The eighth in a series of papers on the application of unipolar leads to the study of problems in electrocardiography.

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From the Medical Division, Montefiore Hospital for Chronic Diseases, Dr. Louis Leiter, Chief; and the Department of Medicine, Lincoln Hospital, Dr. Leander H. Shearer, Director.

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In Lead II, the right arm must be less negative (or more positive) than the left leg, or RA > LL.

In Lead III, the left arm must be less negative (or more positive) than the left leg, or LA > LL.

Therefore, RA > LA > LL.

In other words, in the normal record, the right arm potentials are relatively negative to those of the left arm and left leg, whereas, with downward deflections, a reversal of these conditions has taken place, and the right arm has become relatively positive to both the left arm and the left leg.

Fortunately, we are no longer limited to theoretical analysis of the possible potentials at the extremities, for, with a very simple technique, the actual unipolar extremity potentials can be recorded,[7] and the mechanisms which produce these changes can be more exactly studied.

MATERIAL AND METHOD

In a series of one thousand cases in which both standard leads and unipolar extremity leads were taken, there were fifteen in which the main deflections were downward in the three standard leads. In five of these, there was evidence of enlargement of the right ventricle, or of conditions in which right ventricular hypertrophy might be expected (chronic asthma and pulmonary tuberculosis). One of these patients died, and autopsy confirmed the diagnosis of right ventricular hypertrophy. The other ten were cases of myocardial infarction. In three of these, there was radiographic evidence of ventricular aneurysm.

In addition to these cases, we had the opportunity to study eight other autopsy cases, collected by one of us (S. P. S.), in which QRS pointed downward in the standard leads. One of these patients had multiple myocardial infarcts; the others had pulmonary tuberculosis and merely showed right ventricular hypertrophy or dilatation at autopsy.

Standard leads were taken as usual. For unipolar leads, the technique developed by one of us (E. G.)[7] of obtaining augmented unipolar extremity leads was used. The author's indifferent electrode of zero potential was used for the unipolar leads.[7] Some of the precordial leads were taken with the left leg as the indifferent electrode. The others were taken with the author's indifferent electrode.[7]

RESULTS

Fig. 1, *a*, shows the unipolar extremity leads of a normal subject, for comparison with the other records. Note that the right arm lead is negative (−); the left arm and left leg leads are positive (+).

The cases in which QRS was downwardly directed as a result of right ventricular hypertrophy are shown in Fig. 2, and those in which the cause was myocardial infarction, in Fig. 3. Fig. 2, *d*, is from a case of atypical right bundle branch block in which the QRS in the standard leads was directed downward.[5] This patient had anterior infarction.

On cursory examination, it will be noticed that, as was theoretically predicted, the right arm lead is not only relatively less negative than the

left arm and left leg leads, but the right arm lead tends to be actually (+), and the left leg lead actually (−), in all records.

However, further examination of the right arm lead shows that the (+) deflection is of two forms: (a) a biphasic complex consisting of an initial downward deflection (Q) followed by an upstroke (R), and (b) a (+) deflection in which the initial and main deflection is an upstroke (R).

Examination of the left leg lead also shows two forms of the (−) deflection: (a) a biphasic complex consisting of a small initial upward deflection (r), followed by a deep S, and (b) a deep, initial, downward, main deflection (Q).

Examination of the left arm lead also shows two general types of patterns: (a) a biphasic complex consisting of an initial small upward deflection (r), followed by a deep S, and (b) an initial downward (Q) deflection.

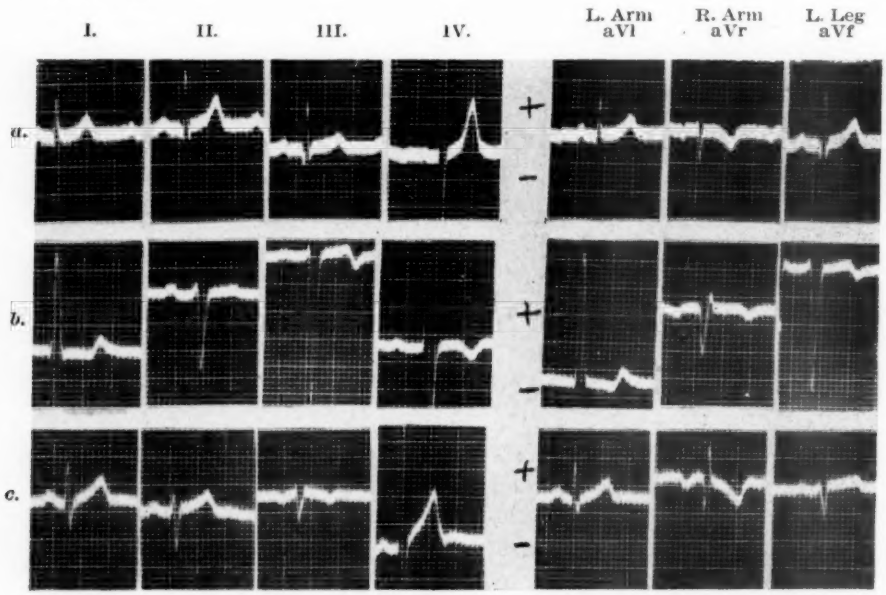

Fig. 1.—*a*, Normal. G. K., 41-year-old man. *b*, Marked left axis deviation. M. Z., 73-year-old man with hypertensive cardiovascular disease. *c*, Marked left axis deviation. R. H., 42-year-old man.

The interpretation of these patterns is as follows:

Right Arm Lead.—A. The biphasic QRS, as we have previously demonstrated, can be produced by both marked right axis deviation and marked left axis deviation.[8, 9]

B. The R type of deflection, as we have also shown, is found only in cases of extensive myocardial damage.[10*] This may occur with both anterior and posterior infarction. However, the exact degree of damage that must take place to cause this is not exactly known.

*See *Addendum.*

Left Leg Lead.—A. The biphasic rS is regularly seen in left axis deviation.[8] We have demonstrated that it also occurs in cases of marked right axis deviation and right ventricular hypertrophy.[9]

B. The deep Q wave is characteristic of posterior infarction.[8, 11]

Left Arm Lead.—A. The biphasic rS is regularly seen in right axis deviation.[8]

B. The Q, with a "coronary," or coved, T wave, is characteristic of anterior infarction.[8, 11] The left arm lead of Fig. 2, *c*, from a case of right ventricular hypertrophy, superficially resembles this pattern.

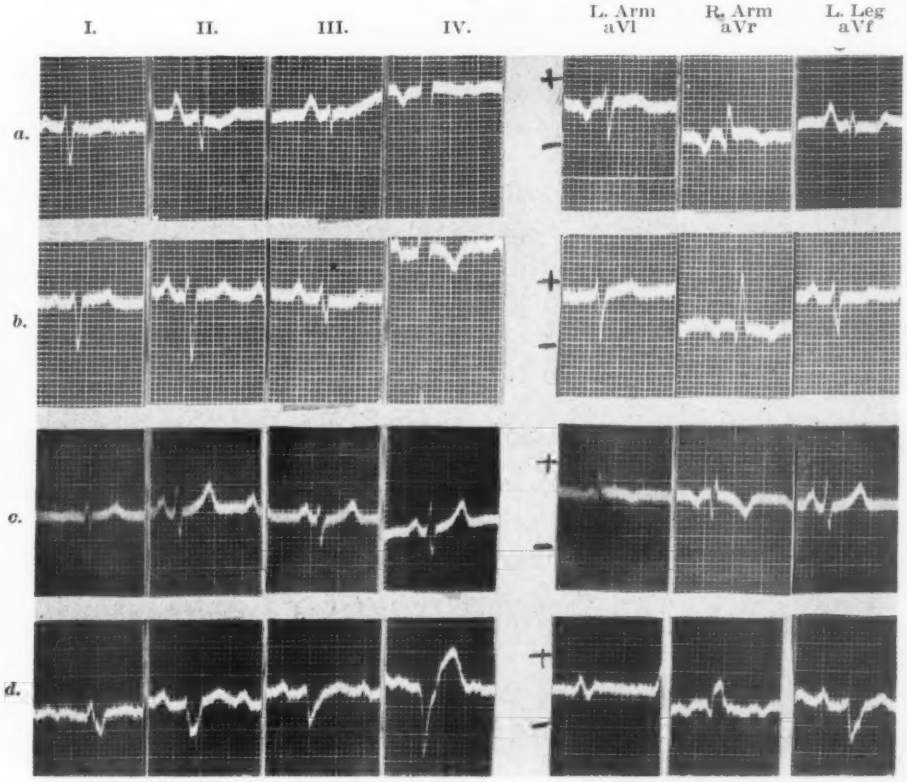

Fig 2.—Downwardly deflected QRS in cases of right ventricular hypertrophy (*a*, *b*, and *c*). Fig. 2*d*, is from a case of atypical bundle branch block. It is not known whether right ventricular hypertrophy was present in this case. *a*, B. K., 59-year-old white man with chronic asthma and emphysema. The patient died, and autopsy revealed the greatly enlarged right ventricle. *b*, K. R., 63-year-old white man with chronic asthma. *c*, S. K., 61-year-old white man with chronic bronchitis and asthma. *d*, W. M., 45-year-old man. Arteriosclerotic heart disease, and anterior infarction.

Furthermore, a small Q_1 is present. A similar pattern was observed in two of our other cases in which there was only right ventricular hypertrophy at autopsy.[3] We made very careful studies of this case; over twenty unipolar leads were taken from all regions of the surface of the body, and there was a gradual transition from the pattern seen in the right arm lead to that seen in the left arm lead as the electrode moved across the upper portion of the body to the left. The change

consisted in a shortening of the initial downward deflection and a decrease in the depth of the T wave. The left arm lead in Fig. 2, *c*, is, therefore, basically similar to the right arm lead. This does not occur in the cases of this type in which there is anterior infarction (Fig. 3, *a*, *b*, and *c*).

The explanation of this unusual condition is as follows: Normally, the heart lies obliquely, so that the right shoulder girdle and the right arm lead face the interior of the heart (the endocardium). Since the endocardium is (–) as the QRS is written, the right arm lead is also (–).

When the heart is very vertical, the right arm lead only partially faces the endocardium, and its potential becomes biphasic (QR).* In such a case, the left arm lead also partially faces the endocardium, and its potential tends to resemble that of the right arm lead.[8, 9] Roentgenograms of this patient's chest confirmed the supposition that he should have a long, narrow heart.

In a case of anterior infarction, the downward deflection of the left arm lead is due to the fact that the left arm lead faces the epicardial surface of the ventricle which has been infarcted.[8]

We thus have the possible interaction of five different factors (left axis deviation, right axis deviation, marked myocardial damage, anterior infarction, posterior infarction) as a cause of these patterns.

Marked right axis deviation, alone, can cause a biphasic right arm lead, a downward left arm lead, usually consisting of an rS, and a downward left leg lead consisting usually of a biphasic rS. This combination will produce a downward deflection in the three standard leads (Fig. 2, *a*, *b*, and *c*).

Marked left axis deviation can cause the biphasic right arm lead and a downward left leg lead consisting of an rS, but the left arm lead is characteristically upward and usually very high. In such a case, Lead I will be tall, and only Leads II and III downward (Fig. 1, *b*). However, if anterior infarction occurs in such a case it will cause marked lowering of the left arm potentials because a Q wave results.[8] This will cause Lead I to point downward, also. Fig. 3, *c*, illustrates such a case. Here there was marked left axis deviation due to the presence of a large ventricular aneurysm, and a downward left arm lead as a result of the anterior infarction.

Extensive myocardial damage, either due to anterior or posterior infarction, results in a (+) right arm lead and a Q wave in the left arm or the left leg lead, depending on the location of the infarct. This alone is not sufficient to cause a downward QRS in the standard leads, unless both anterior and posterior infarction are present (Fig. 3, *a* and *b*). In such a case, there will usually be a Q wave in Leads I, II, and III.

Anterior infarction, alone, causes only a lowering of the left arm lead (due to the Q wave). Ordinarily, the right arm lead remains (–) and

*See *Addendum.*

the left leg lead (+). However, as was mentioned above, the addition of marked left axis deviation causes changes in the latter two leads, and a downward deflection in the standard leads results (Fig. 3, *c*).

Posterior infarction, alone, causes only a lowering of the left leg lead (due to the Q wave[8]). The right arm lead remains (−) and the left arm lead (+). Marked right axis deviation in such a case will cause a downward left arm lead and a biphasic right arm lead, and so produce a downward deflection in the standard leads. Fig. 3, *d*, approaches such a pattern.

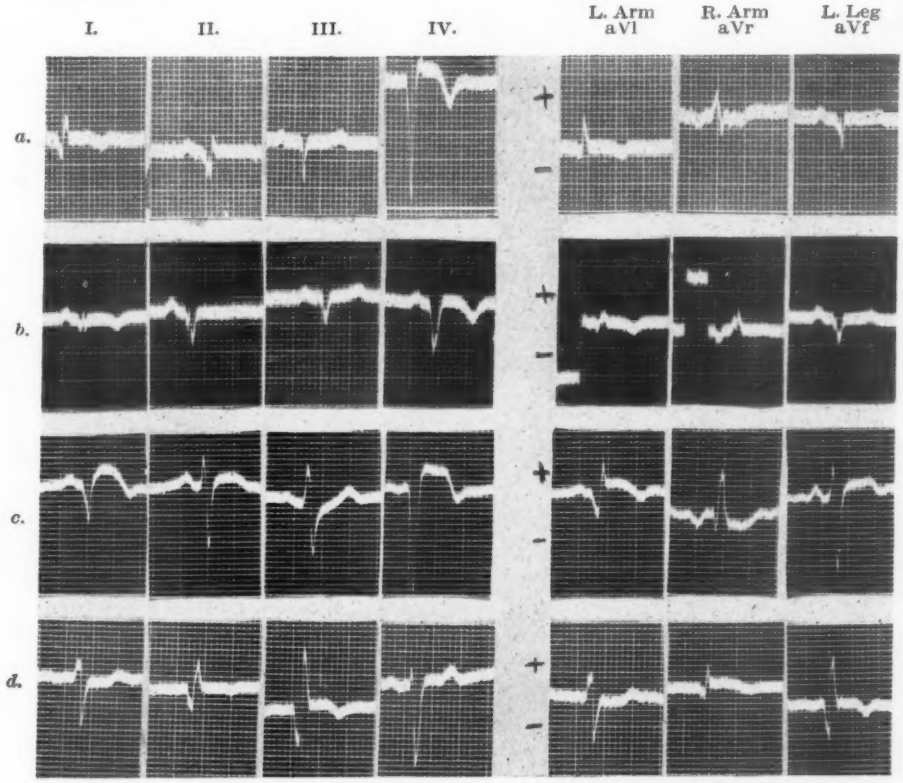

Fig. 3.—Downwardly deflected QRS in cases of myocardial infarction. *a*, B. Z., 55-year-old white man with signs of anterior and posterior myocardial infarctions. *b*, L. R., 53-year-old white woman with signs of anterior and posterior myocardial infarctions. *c*, C. H., 59-year-old white man with anterior infarction and marked left axis deviation due to aneurysm of the left ventricle. *d*, W. N., 54-year-old white man with posterior infarction and aneurysm of the left ventricle.

Combined anterior and posterior infarction produces a Q in both the left arm and left leg leads, but does not necessarily cause reversal of the normal (−) potential in the right arm lead, which is necessary to produce the downward deflection in the standard leads. When, as was pointed out above, the right arm becomes (+) because of the marked myocardial damage, the downward pattern in the standard leads occurs (Fig. 3, *a* and *b*). Theoretically, marked right or left axis deviation in a case of anterior and posterior infarction could also cause this pattern.

In the case of atypical right bundle branch block (Fig. 2, *d*) there was a biphasic right arm lead, and the pattern may therefore be considered as also due, at least, in part, to marked axis deviation.

To summarize, a downward QRS in the three standard leads may occur as the result of: (1) Marked right axis deviation. This is usually due to right ventricular hypertrophy. (2) Anterior infarction in association with marked left axis deviation. (3) Posterior infarction in association with marked right axis deviation. (4) Extensive myocardial damage due to both anterior and posterior infarction.

DISCUSSION

It has been said[1] that downward deflection of QRS in the standard leads cannot be interpreted by the Einthoven triangle concept. A simple illustration will prove the fallacy of this:

Fig. 4 gives the range of potentials for each of the unipolar extremity leads. Normally, the electrical axis (at the instant the peak of the QRS complex is being written) lies in a range of 0° to + 90°. Thus, if the electrical axis were +40° (point *A* in Fig. 4), it can be seen that the left arm lead would be (+), the right arm lead (−), and the left leg lead (+),

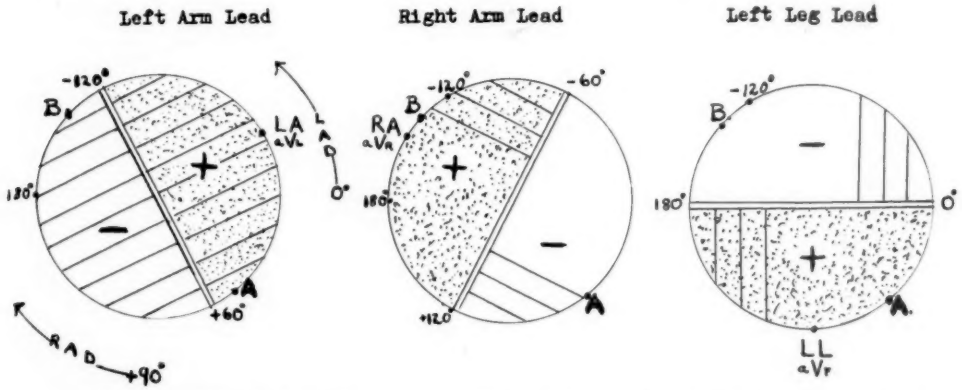

Fig. 4.—Graphs showing the relationships between the electrical axis and the polarities and potentials of the unipolar extremity leads. The diagonal and vertical lines indicate how the amplitudes of the records vary when the electrical axis changes.

which is normal. However, if the electrical axis were −130° (point *B* in Fig. 4), the left arm lead becomes (−), the right arm lead (+), and the left leg lead (−), (Fig. 4). In other words, cases in which there is a downward deflection in the three standard leads are merely examples of extreme degrees of axis deviation. From Fig. 4, one can see that the electrical axis of such records must fall within the range of −120° to 180°.

There is one more point to be discussed. It was pointed out above that marked right axis deviation, *without* myocardial infarction, can cause the downwardly deflected QRS. Study of Fig. 4 shows that the electrical axis in such a case must have rotated clockwise to reach at

least 180° (where the left leg lead becomes isoelectric again). Theoretically, therefore, the possibility exists that extreme left axis deviation, without myocardial infarction, might also be able to produce a downwardly deflected QRS. In such a case, the electrical axis would have to rotate counterclockwise to at least −120° (where the left arm lead becomes isoelectric again). Although we have not seen any unequivocal cases of this type, Fig. 1, *c*, illustrates a case of left axis deviation in which this tendency was present.

CONCLUSIONS

Normal and abnormal standard lead electrocardiograms ordinarily have the QRS in one or more leads directed upward. This is due to the fact that, although the range of the electrical axis of these records encompasses a wide area, it does not completely circle the 360°.

However, cases are occasionally observed in which the electrical axes do cover this range. Such cases fall into the following groups when studied with unipolar extremity leads: (1) Marked right axis deviation, usually due to right ventricular hypertrophy. In most of these cases there is an S wave in the three standard leads. Occasionally, a small Q_1 is observed in association with a small QRS_1. (2) Anterior infarction in association with marked left axis deviation. Standard leads show a deep Q_1 and a deep S_2 and S_3. (3) Posterior infarction in association with marked right axis deviation. Standard leads show the Q_2 and Q_3 which are characteristic of posterior infarction. (4) Combined anterior and posterior infarction. Standard leads show a Q_1, Q_2, and Q_3.

In these cases, the effect of axis deviation is particularly apparent in the unipolar extremity leads, especially the right arm lead. In the cases in which a shift in the long axis of the heart is responsible wholly, or in part, for the pattern, the right arm lead has a biphasic QR deflection.

In the cases in which extensive myocardial damage, and *not* any actual shift in the long axis of the heart, is responsible for the pattern, the right arm lead has a (+) R deflection.

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ADDENDUM

Recent studies of ours, using multiple unipolar leads from the surface of the body in cases with a downward QRS, show that the biphasic QRS of the right arm lead can be explained by backward displacement of the apex of the heart, so that the right arm lead records potentials which are ordinarily found over the upper back. If this occurs in a markedly vertical normal heart, in addition to a biphasic right arm lead, the left leg will face the right ventricle, instead of the left ventricle, and will point downward, as will Leads I, II, and III.

Studies in cases in which the right arm lead has an initial main (+) deflection indicate that this may be due in part to forward displacement of the apex of the heart, so that the (+) right arm lead is similar to unipolar leads from the right upper chest and sternal regions. Although we had previously found this only in cases of infarction, we recently had one case of right ventricular hypertrophy in which this occurred.

PROPHYLACTIC USE OF LANATOSIDE C IN AURICULAR PAROXYSMAL ARRHYTHMIAS

RALPH M. TANDOWSKY, M.D.
LOS ANGELES, CALIF.

INTRODUCTION

DIGITALIS preparations, particularly the most recently isolated glycosides, have been used for some time in the abortive treatment of the paroxysmal auricular arrhythmias.[1] Published accounts of this therapy pay little attention to the use of these digitalis bodies as a means of preventing frequent recurrences of these disturbing arrhythmias. This report is concerned, in the main, with this phase of therapy. Although the data presented are meager, the results obtained offer encouragement for further study.

The use of lanatoside C* orally in preference to other preparations of digitalis seems reasonable because this drug acts with rapidity, yet with minimal toxic effect, and retains its pharmacologic potency in vivo for at least twenty-four hours.[2, 3] The effect of this drug has been demonstrated both electrocardiographically and clinically[4] to be without variability, whereas other preparations of digitalis act with marked inconsistency.[5] Furthermore, the toxic effects of this drug, when administered over a prolonged period of time, are less than those of other digitalis preparations in common use.[6]

MECHANISM OF ACTION

Digitalis and its derivatives have a tendency to slow the rate of the heart in auricular paroxysmal arrhythmias, and often restore normal rhythm. The effect is not unlike vagal stimulation. Slowing of the heart rate without abolition of heterogenetic auricular activity, as demonstrated by the electrocardiogram (Figs. 1 and 2), may be noted either before the termination of an attack or as a fleeting change during the course of the arrhythmia. Digitalis acts directly on the heart muscle and indirectly by stimulating the vagus nerves. In the presence of auricular fibrillation and flutter, the increase in "circus rate" attributed to the action of this drug is apparently due to increased vagal tone, which shortens the refractory period of auricular muscle. The slowing effect on the ventricle is apparently due to both direct and indirect depression of conductivity in the atrioventricular node. In the presence of paroxysmal auricular tachycardia and flutter, the

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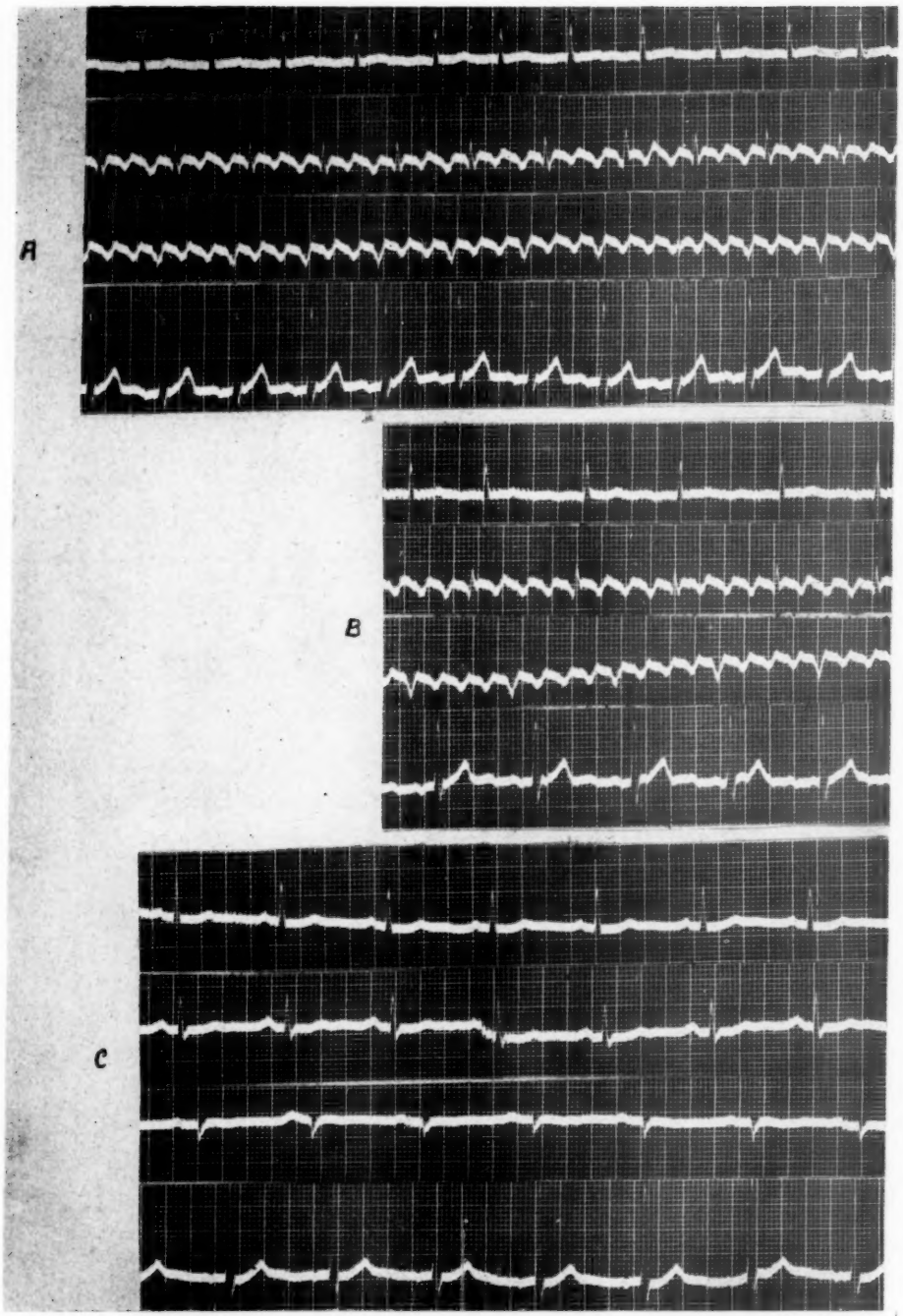

Fig. 1.—Lanatoside C in auricular flutter; Case 1. *A*, Four standard leads prior to administration of drug. Auricular rate, approximately 250 per minute. Ventricular rate, 100 per minute. *B*, Taken fifteen minutes after the administration of 1.6 mg. of lanatoside C intravenously. Auricular rate, approximately 250. Ventricular rate, 80. Slight sagging of S-T can be noted in Lead IVF. *C*. Taken two hours after administration of lanatoside C. Auricular rate, 70; ventricular rate, 70. Sagging of the S-T segment in Leads I, II, and IVF.

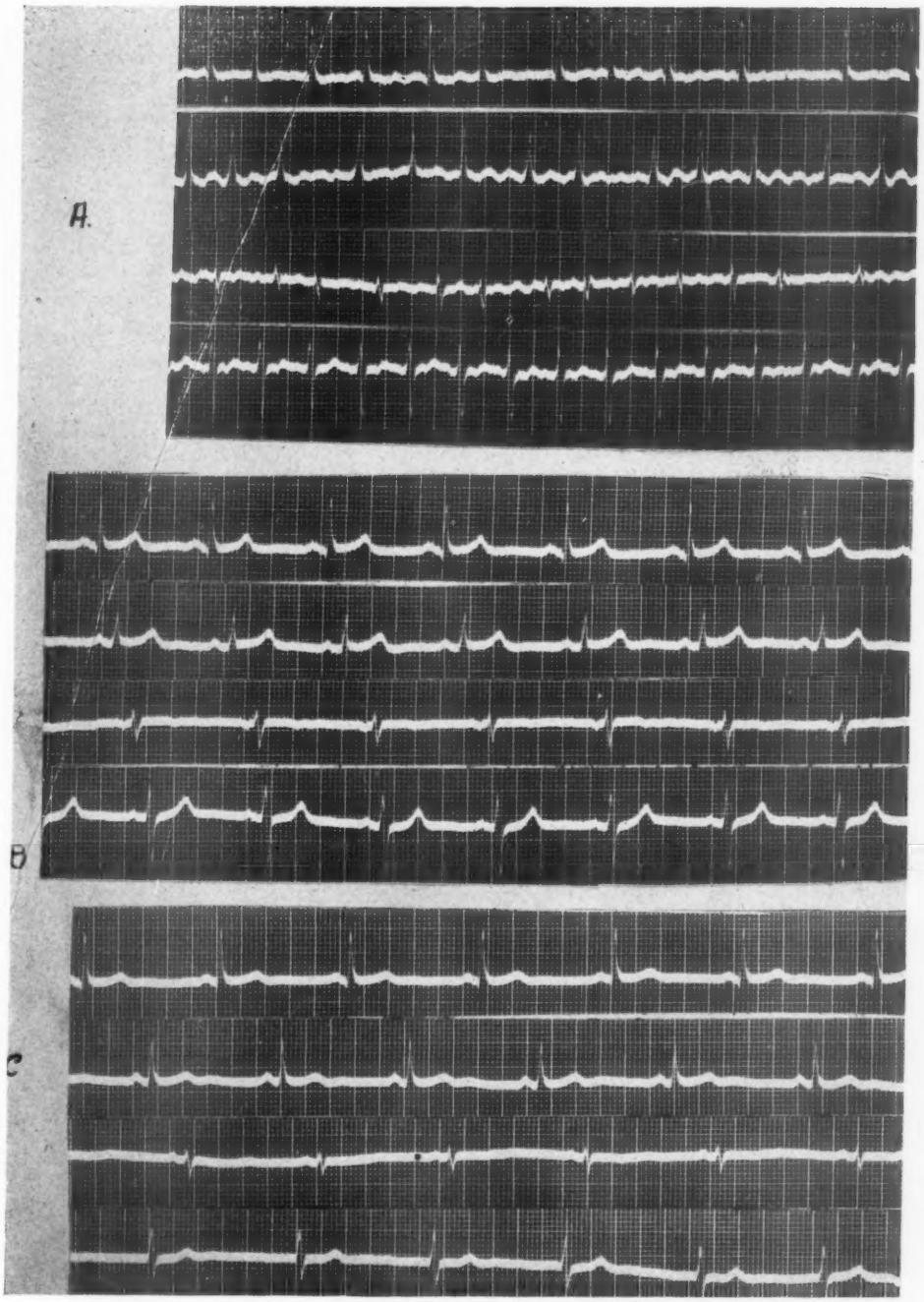

Fig. 2.—Lanatoside C in auricular flutter; Case 5. *A*, Taken prior to administration of drug. Auricular rate, approximately 250 per minute. Ventricular rate, approximately 122 per minute. *B*, Taken forty minutes after the administration of 1.6 mg. lanatoside C intravenously. Auricular rate, 62. Ventricular rate, 62 per minute. Note marked sinus effect with re-establishment of sinus rhythm. *C*, Taken six months after initial paroxysm. Patient receiving 0.5 mg. lanatoside C daily. Note minimal digitalis effect on the S-T segments.

effect of digitalis cannot very well be due to shortening of the refractory period of auricular muscle. Its effect must depend on its nodal action, or on some unknown action on the neuromuscular mechanism. It has been shown that digitalis acts upon auricular muscle by increasing its effective refractory period and by depressing its conductivity.[7-9] The abolition of a paroxysm of tachycardia or flutter cannot well be due to this action, for the indirect vagal action of the drug upon auricular muscle and the effects of digitalization and vagal stimulation in these arrhythmias are similar. Little is known regarding the action of digitalis on the rate of impulse formation in auricular muscle. It seems logical to assume, with the limited knowledge at our disposal, that digitalis abolishes these arrhythmias by exerting some effect on the nodal tissues.

Clinical observation has proved the usefulness of rapidly acting digitalis glycosides in the therapy of supraventricular arrhythmias, and, although their mode of action is still somewhat obscure, further clinical investigation offers the only method that will reveal the unknown physiologic factors. The frequency of recurrence of these arrhythmias is difficult to explain, but their appearance demands an efficient therapeutic investigation. It is hoped that this mode of therapy will receive more attention, and that the procedure herein briefly outlined will offer a basis for further study.

PROCEDURE

With the exception of one, those under observation were known to have had recurrent attacks of auricular paroxysmal tachycardia and flutter. This was confirmed electrocardiographically. The immediate attack received first consideration, and was treated by giving lanatoside C in a dose of 1.6 mg. intravenously. After cessation of the paroxysm, the drug was given orally, and the dose was determined by electrocardiographic criteria. It was felt that, when minimal sagging of the RS-T segment in one or more leads was present, there was adequate prophylactic saturation with the drug. This minimal effect on the electrocardiogram has been consistently demonstrated when lanatoside C has been administered.[9] It has been noted that, when this drug is given over a prolonged period of time in amounts in excess of that which produces the minimal electrocardiographic effect, premature ventricular contractions often produced disturbing symptoms. Each patient in this series was seen at least once every two weeks throughout the entire period of study. Careful historical data were gathered at each visit, particularly relative to untoward symptoms, produced either by the drug or by the recurrence of the arrhythmia. Those under observation were all ambulatory, and were allowed to carry on their normal environmental routines. In some, accessory medication was administered when necessary, and consisted, in the main, of mild sedatives such as the barbiturates or bromides.

RESULTS OF STUDY

Of the eight patients observed in this study, six had one or more paroxysms of auricular flutter, and two had frequent attacks of par-

TABLE I. PROPHYLACTIC USE OF LANATOSIDE C IN AURICULAR PAROXYSMAL ARRHYTHMIAS DATA ON CASES OBSERVED

NUMBER	DIAGNOSIS	AGE (YR.) SEX	ASSOCIATED CARDIAC DISEASE	PERIOD OF OBSERVATION (MO.)	DRUG TREATMENT OF PAROXYSMS	NUMBER OF PAROXYSMS IN 12 MONTHS PRIOR TO MEDICATION	NUMBER OF PAROXYSMS WHILE UNDER OBSERVATION	ACCESSORY MEDICATION	ECG EFFECT	UNTOWARD EFFECTS	DOSAGE MG. DAILY
1	Auricular flutter	51 M	0	8	1.6 mg. lanatoside C	6	0	Phenobarbital 1 grain daily	+	V.P.C.*	0.5
2	Auricular flutter	53 M	Coronary arteriosclerosis	14	1.6 mg. lanatoside C	4	1 Alcoholic debauch	Thiamin 30 mg. daily	+	0	0.5
3	Auricular paroxysmal tachycardia	62 M	Old anterior infarction	24	1.6 mg. lanatoside C	3	1 Discontinued drug 1 week	1½ grains phenobarbital daily	+	V.P.C.	0.5
4	Auricular paroxysmal tachycardia	32 F	0	5	6.5 mg. lanatoside C	8	1 Following laparotomy	2,000 R.U. estrogenic substance weekly	+	0	0.5
5	Auricular flutter	72 M	Coronary arteriosclerosis	14	1.6 mg. lanatoside C	6	0	Bromides 30 grains daily	+	0	0.5
6	Auricular flutter	49 F	0	30	1.6 mg. lanatoside C	4	0	2,000 R.U. estrogenic substance weekly	+	0	0.5
7	Auricular flutter	32 F	Rheumatic mitral and aortic endocarditis	32	1.6 mg. lanatoside C	3	0	Phenobarbital 1 grain daily	+	V.P.C.	0.5
8	Auricular flutter	52 M	Coronary arteriosclerosis	4	1.6 mg. lanatoside C	0	0	0	+	0	1.0

Totals

DIAGNOSIS	AVERAGE AGE (YR.)	ASSOCIATED DISEASE	AVERAGE TIME OBSERVED	AVERAGE	AVERAGE	DRUGS	ECG	PROPHYLACTIC DOSAGE
Auricular flutter 6 Auricular paroxysmal tachycardia 2	50.3	None 3 Coronary arteriosclerosis 3 Old infarction 1 Rheumatic 1	15 Months	4.2	0.37	Phenobarbital 3 Bromides 1 Estrogenic substance 2 Thiamin 1	Sagging RS-T 7 Flat T_2 1 case	0.5 mg. daily 7 1 mg. daily 1 case

*V.P.C.=Ventricular premature contractions.

oxysmal auricular tachycardia. With the exception of three, there was evidence of organic heart disease, and this, in the main, indicated coronary artery disease. One patient had rheumatic carditis. The average age was 50.3 years. Five were men; three were women. The average time of observation was approximately fifteen months. Each patient was seen during a paroxysm, and this paroxysm was treated with the full digitalizing dose of lanatoside C (1.6 mg.) intravenously; in one case the drug was given orally (6.5 mg.) over a period of forty-eight hours. Response to this medication, with re-establishment of normal sinus rhythm, occurred in all cases within a period of forty-eight hours. Immediately after the administration of the drug a primary ventricular slowing effect was noted (see electrocardiograms).

It is interesting that, prior to the lanatoside C medication, the entire group averaged 4.2 paroxysms in a twelve-month period. Maintenance therapy with lanatoside C over an average period of fifteen months reduced the incidence of recurrence to 0.37. The maintenance dose in all but one case did not exceed 0.5 mg. daily. Three of the patients had one recurrence of tachycardia during the period of observation. In one case a paroxysm followed an alcoholic debauch, in another it followed discontinuance of the drug for a period of one week, and in the third the arrhythmia made its appearance immediately after laparotomy for gall bladder disease. The recurrences in all three were of extremely short duration, and each abated without special medication.

The electrocardiographic effect of lanatoside C was observed in all of the cases, and this effect at no time abated until the drug was discontinued for a period of three days or more. This effect consisted of a slight sagging of the RS-T segment, with or without flattening of the T wave. In three instances, because of general apprehension, it was necessary to give 1½ grains of phenobarbital in divided doses. One patient received 30 grains of triple bromides daily, and two women, because of climacteric symptoms, received weekly injections of estrogenic substance. One patient, because of impending peripheral neuritis, received 30 mg. of thiamin daily.

The only untoward effect that could possibly be attributed to the use of this drug prophylactically was the occurrence of ventricular premature contractions in three cases.

SUMMARY

It appears that lanatoside C in some unknown way reduced the recurrence frequency of paroxysmal auricular tachycardia and flutter in eight cases from 4.2 in a twelve-month period to 0.37 in a fifteen-month period, following the use of the same drug in full digitalizing dosage at the onset of an initial paroxysm. The amount of drug used prophylactically did not exceed 0.5 mg. daily in seven cases; in the eighth the dosage was 1 mg. Electrocardiographic evidence of the effect of the drug on the RS-T segment and T wave was noted. Associated

cardiac lesions in no way altered the result. The only untoward effect was the appearance, from time to time, of ventricular premature contractions. In three instances one paroxysm occurred recurrently, and in each of these a definite causative factor was established. The results obtained constitute evidence of the value of this drug for prophylactic therapy in cases of paroxysmal auricular tachycardia and flutter.

CONCLUSIONS

1. Lanatoside C appears to be of value prophylactically in the treatment of paroxysmal auricular tachycardia and flutter, provided the therapy is commenced by giving it intravenously to stop a paroxysm.

2. The effective prophylactic dose varied from 0.5 to 1 mg. daily.

3. Characteristic electrocardiographic changes may be used as a criterion of the effect of the drug.

4. Lanatoside C, because of properties discussed in this article, may be considered preferable to other digitalis preparations for prophylactic therapy.

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SOME OBSERVATIONS ON THE SYNDROME OF SHORT P-R INTERVAL WITH LONG QRS

E. R. Movitt, M.D.
San Francisco, Calif.

THE electrocardiographic pattern of a short P-R interval with long QRS has been well established, and many cases have been reported. It is the purpose of this article to review briefly the literature on the subject and add another case in which there were certain unusual features not heretofore described.

REVIEW OF LITERATURE

Although the first case was described by Wilson,[1] in 1915, the next in 1921, by Wedd,[2] and the third in 1929, by Hamburger,[3] credit for the first systematic study goes to Wolff, Parkinson, and White,[4] who collected and reported eleven cases and established the anomaly of short P-R intervals in association with prolonged and aberrant QRS complexes as a clinical entity. Their work stimulated interest over all the world, with the result that there has been a steady increase in the number of recorded cases since 1930. Pezzi[5] reported three cases in 1931; and Holzmann and Scherf[6] reported two in 1932. Wolferth and Wood[7] reported ten cases, and Sigler,[8] one case, in 1933; Roberts and Abramson[9] reported one case, Faxen,[10] one, and Tung,[11] five, in 1936; in the same year Cossio, Berconsky, and Kreutzer[12] reviewed twenty-seven cases from the literature, added seven of their own, and analyzed the group statistically from the standpoint of age, sex, type of tachycardia, presence or absence of coincidental organic heart disease, and change to a normal electrocardiographic pattern. In 1937, Sprague[13] reported one case and Bishop[14] described another, summarizing to date the literature on the subject. Additional cases were reported by Pines[15] and Moia and Inchanspe,[16] in 1938; in 1940 by Hunter, Papp, and Parkinson,[17] again by Wolferth and Wood,[18] and also by Levine and Beeson,[19] in 1941; in 1942 and 1943 one case was reported by Dassen,[20] one by Fox, Travell, and Molofsky,[21] one by Wood, Wolferth, and Geckeler,[22] and another by Clagett.[23]

In the first case, reported by Wilson,[1] that of a man, aged 23 years with attacks of paroxysmal tachycardia for eleven years, the characteristic electrocardiographic abnormality appeared on stimulation of the vagus nerve, and, when spontaneously present, could be abolished by the administration of atropine. A somewhat similar electrocardiographic anomaly was reported by Wedd,[2] and apparently also by Hamburger.[3]

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In the latter case, that of a child aged 4½ years who had an acute febrile illness, the author assumed that the bundle branch block occurred as the result of the respiratory infection, and the short P-R interval was interpreted as part of a nodal tachycardia.

Thus the original observation by Wilson remained unnoticed for a period of fifteen years, until 1930, when Wolff, Parkinson, and White[4] made similar observations. In the group of cases presented by these authors the following characteristics were noted: (1) The patients were usually young, healthy persons without evidence of organic heart disease, except for two cases in which organic heart disease was considered as purely coincidental. (2) Their electrocardiograms showed short P-R intervals (0.1 second or less) and ventricular complexes with certain characteristics suggesting bundle branch block (the QRS complexes were widened and slurred and the T waves might be opposite in direction from the main deflection of QRS). (3) In some cases both the P-R interval and the ventricular complex suddenly reverted to normal without change in contour or direction of the P waves. This might occur spontaneously or when the heart rate was increased by exercise or by atropine administration. When the heart rate slowed the abnormal characteristics might return. Vagal stimulation effected a return of aberrant complexes in one case. (4) Patients in this group were particularly liable to attacks of paroxysmal supraventricular tachycardia, during which the ventricular complexes invariably assumed a normal configuration. Thus, a syndrome of short P-R interval with long QRS became established as a clinical entity.

In the group of cases studied by Wolferth and Wood,[7] the following additional features were stressed: (1) The time from the beginning of the P wave to the end of the QRS complex was well within normal limits, despite the aberration of the ventricular complex. (2) If the P-R interval lengthened, the QRS complex simultaneously shortened to an equal extent. Consequently, in a given case the period from the beginning of P to the end of QRS remained substantially the same throughout, whether the electrocardiogram was normal or abnormal.

In addition to atropine, quinidine was found by Roberts and Abramson[9] to change the contour of their patient's electrocardiogram from abnormal to normal, and a somewhat similar effect was produced in one of the cases reported by Scherf and Schonbrunner[24] by the administration of large doses of digitalis, which caused disappearance of the abnormal QRS complex. On the contrary, digitalis uniformly produced further prolongation of the abnormal QRS in the case studied by Fox, Travell, and Molofsky.[21] Finally, Hunter, Papp, and Parkinson reported cases in which the QRS complexes were intermediate in shape between the normal and the aberrantly long QRS complexes.

This syndrome usually occurs in young persons, and is more common in males than in females. It has been found in persons of all ages (from early childhood to the seventh decade), but most frequently in the

second, third, and fourth decades. Not infrequently the history dates back to puberty or earlier, when the patient first began to experience periodic attacks of palpitation. However, in a number of cases palpitation was never experienced. Among the arrhythmias which these persons are so prone to develop, paroxysmal auricular tachycardia ranks first; auricular fibrillation occurs considerably less frequently. Lately a few cases in which there were paroxysms of ventricular tachycardia have been described.[19] During the attacks of tachycardia of supraventricular origin the electrocardiogram invariably shows normal QRS complexes (except in the case here reported, which is the only exception so far observed).

The data on the effects of atropine and exercise are conflicting. Although in some cases these methods of vagus inhibition abolish the electrocardiographic abnormality, this is not universal. Similarly, the effect of digitalis is not constant.

Although there are a few cases in which organic heart disease was present, the type of organic involvement was quite diverse, and the organic heart disease, when encountered, was probably purely coincidental.

The fact that the syndrome is most frequently found in young persons, and that there are some cases in which reversal to the normal electrocardiographic pattern has been observed with advancing age—as in Case 9 of Wolferth and Wood[7] and Cases 3 and 8 of Wolff, Parkinson, and White[4]—suggests that certain persons may "outgrow" their electrocardiographic anomalies, i.e., the mechanism responsible for the short P-R interval and aberrant QRS complex becomes, for some unknown reason, less capable of functioning with advancing years.

The abundance of reported cases is paralleled only by a propensity to expound the various theories which have been advanced to explain the electrocardiographic anomaly. No attempt will be made here to discuss all these hypotheses, inasmuch as excellent reviews of the subject have already appeared.[7, 17, 18] Only two views will be briefly discussed, one because of its historical interest (Wolff, Parkinson, and White), and the other (Wolferth and Wood) because it appears to have established the explanation of the syndrome on a more sound basis both experimentally and clinically. The case presented here is analyzed in the light of the latter theory.

Wolff, Parkinson, and White,[4] who have the credit for the first systematic study of this electrocardiographic anomaly, believed that the phenomenon was one of regular sinus rhythm with functional intraventricular block. The latter was thought to be a vagal effect induced by excess vagal tone, slowing conduction through the bundle or one of its branches. They held the view that the syndrome was a vagal effect, for, in their cases, reversal to the normal electrocardiographic pattern took place on suppression of the vagal influence by exercise or atropine. In addition, in one of their cases the abnormal electrocardiogram could

be reproduced by vagal stimulation, and thus they repeated the original observation made by Wilson in 1915. However, in cases reported by other workers, the effect of vagal release on the electrocardiogram with a short P-R interval and long QRS has not always been the same. Besides, this hypothesis would imply a "paradoxical effect" of vagus tone, with the simultaneous exercise of two diametrically opposed influences, one accelerating conduction between auricles and ventricles, resulting in shortening of the P-R interval, the other retarding conduction through the bundle of His in the ventricles, giving rise to the lengthening and aberrant configuration of the QRS complex. The theory also implies that the vagus nerve may influence intraventricular conduction. Changes in the ventricular complex during stimulation of the vagus nerve in dogs were produced by Hering,[25] but they were in the amplitude, not the duration, of the QRS complex. Ritchie[26] similarly found that, in human subjects, stimulation of the vagus nerve did not effect any change in the duration of the QRS complex.

Wolferth and Wood[7] presented ten cases, in none of which did "vagal release" with atropine cause reversal to a normal electrocardiogram. Neither did vagus stimulation lead to return of the abnormality in the case in which spontaneous restoration of the normal P-R interval and QRS complex occurred. These observations, in conjunction with certain other considerations, discredited the theory of Wolff, Parkinson, and White, and started these authors on a search for a different explanation. They postulated that there was some aberrant conduction bundle between the auricles and ventricles, and that it was able to transmit impulses. With this as a premise, they argued that the syndrome represented normal sinus rhythm, with conduction by a direct and shorter pathway between the sinus node and the ventricles, which resulted not in block or delay, but in an early arrival of the auricular impulse in the ventricular muscle. The abnormality was present when the impulses passed through this aberrant path, and the normal pattern was restored when the impulses returned to the normal pathway. They found support for their theory in the report of Kent,[27] who described a structure bridging the auriculoventricular groove at the right lateral border of the heart of the rat, connecting the right auricle and right ventricle, and subsequently referred to as the bundle of Kent. Lewis discredited the idea that any such bundle would be capable of transmitting impulses from auricle to ventricle, and the bundle of Kent temporarily fell into disrepute, only to be recently revived in this country by Wolferth and Wood, and independently in Germany by Holzmann and Scherf.[6]

Wolferth and Wood,[7, 18] firmly believe that the bundle of Kent or "some analogous structure" offers a satisfactory explanation of the phenomenon of short P-R interval and long QRS. They cite some rather convincing evidence in support of their view: (1) The shortness of the P-R interval is due to the short, direct pathway from auricle to ventricle.

(2) The premature invasion of a certain section of the ventricular muscle by this impulse causes a lengthening of the QRS complex at the expense of the P-R interval. (3) In some cases conductivity in the aberrant bundle may not be highly developed. Consequently, when impulses bombard it at a rapid rate, as during paroxysmal tachycardia, it may fail to function. This seems to offer an explanation for the transition from abnormal to normal complexes which is usually observed during the periods of supraventricular tachycardia. (4) Since Kent showed in rats that retrograde conduction was possible through the "right lateral bundle," therefore, "under certain circumstances a retrograde impulse in these individuals might travel from ventricle to auricle at a time when the physiological state of the auricular muscle would favor the inception of an abnormal rhythm." Thus the mechanism of production of arrhythmias as a part of the syndrome was explained. (5) In their cases the authors observed that, with change from the short P-R interval and long QRS complex to a normal P-R interval and QRS complex, the duration of the interval from the beginning of the P wave to the end of the QRS complex tended to remain constant. On the basis of their theory the interpretation of this particular observation would be dependent on the fact that, since conduction through the junctional tissues (the node of Tawara and the bundle of His) is not interfered with, the variable factor of early aberrant conduction from auricles to ventricles would be responsible for alteration in the duration and form of the initial portion of the ventricular complex in direct correspondence with the prematurity of arrival of the aberrant impulse in the ventricular muscle. (6) If early transmission of the impulse by way of Kent's bundle is responsible for this syndrome, there should be definite asynchronism in the contraction of the two ventricles. Evidence of such asynchronism the authors find in the electrocardiograms (aberrant, slurred, long QRS complexes), in the marked reduplication of the first heart sound which was noted in two of their cases, and in the study of jugular phlebograms. Although at first they held that the right ventricle was the first to be activated,[7] in conformance with the anatomic observations of Kent, later[18] the authors conceded that in some cases the left ventricle could be activated first. This might necessitate revision of ideas concerning the anatomic location or locations of the aberrant pathway.

The theory of Wolferth and Wood finds support in recent observations of both anatomic and physiologic nature. Glomset and Glomset[28] maintained that they were able to demonstrate accessory neuromuscular connections between the auricles and ventricles, and the hypothesis of aberrant auricular conduction found experimental support in the work of Butterworth[29] and Butterworth and Poindexter,[30] who short-circuited the normal conduction system through an amplifier and produced ventricular asynchronism with the electrocardiographic picture of short P-R interval and long QRS. At the same time, reversal of transmission

from ventricle to auricle caused typical auricular tachycardia, thus lending weight to the theory of Wolferth and Wood on the origin of paroxysmal tachycardia in this syndrome. Finally, in 1943, Wood, Wolferth, and Geckeler,[22] by anatomic examination of the heart of a child who had had this syndrome, were able to demonstrate an accessory bundle.

If we accept the aberrant pathway explanation, the demonstration that there is vagal influence in some cases may be interpreted to signify that, with increase in vagal tone, conduction through the normal junctional tissue is slowed or suppressed, and then proceeds through the aberrant bundle. With abolition of increased vagal tone in selected cases by means of exercise or atropine, conduction returns to the junctional tissue of the node of Tawara and the bundle of His. Wolferth and Wood thought that the vagus was a factor in determining whether or not the syndrome was present, depending on the influence of the vagus nerve on cardiac rate "so that if the cardiac rate were rapid the accessory tract might fail to conduct, whereas if it were slower this tract might be able under such circumstances to transmit an impulse."

REPORT OF CASE

W. A., a 57-year-old white American, a motor mechanic by occupation, was admitted to the hospital June 16, 1943, complaining of dyspnea. He had been in this hospital in 1941 for treatment of an upper respiratory tract infection, and stated that he left the hospital feeling well and continued in good health until about a year prior to this admission, when he first noticed dyspnea on lifting objects weighing up to 60 pounds. The exertional dyspnea became progressively more marked until, during the preceding few months, he would get breathless when he walked at a moderate pace on level ground. Three weeks prior to admission he had to give up his work and stayed around the house. He became subject to attacks of paroxysmal nocturnal dyspnea. A few days before admission he had a fainting spell not preceded by any aura and not accompanied by any convulsions, tongue biting, or loss of sphincter control. On the day of admission he went to a doctor who called his attention to the fact that his legs were swollen; he had failed to notice this himself. There was no history of any anginal pain. Except for the usual childhood diseases, he gave no history of any other serious illnesses. He stated that he had enjoyed good health all his life. He was operated on for a dislocated semilunar cartilage in the left knee in 1933. He denied venereal infection.

The patient was a well-developed, obese white man who was slightly dyspneic at rest and had some cyanosis. The heart borders could not be percussed because of the thick chest wall. The heart tones were of poor quality and distant. The heartbeat was rapid and irregular. No murmurs were heard. The radial pulse was of poor quality and irregular, with a pulse deficit of about 50. The radial arteries were not palpably thickened. The blood pressure was 130/90. There was dullness at the bases of both lungs, with some diminution in breath sounds, but without any râles. The liver was enlarged and slightly tender; its edge extended three to four fingerbreadths below the costal margin. There was moderate edema of both legs up to the knees.

Urinalysis showed the presence of 1 plus albumin and occasional casts. The hemoglobin was 14.6 grams. The leucocyte count was 12,550, with 65 per cent polymorphonuclear leucocytes. The blood serologic reactions were negative. A roentgenogram of the chest showed cardiac enlargement; the greatest transverse diameter of the cardiac silhouette measured 17.5 cm. inside the rib cage of 30.5 cm. There was a little mottled central lung density which was interpreted as evidence of passive congestion. The electrocardiogram is reproduced in Fig. 1.

Although clinically it was thought that the patient had auricular fibrillation with a ventricular rate of about 170, the electrocardiogram was at first interpreted as indicating ventricular tachycardia. It may be mentioned in passing that the tracing was examined hurriedly in the dark room immediately after developing. The patient received 30 grains of quinidine within a period of about eighteen hours, and the following morning was found to have regular rhythm with a rate of 80. Unfortunately, no electrocardiogram was taken at that time. A maintenance dose of 9 grains of the drug a day was administered without any

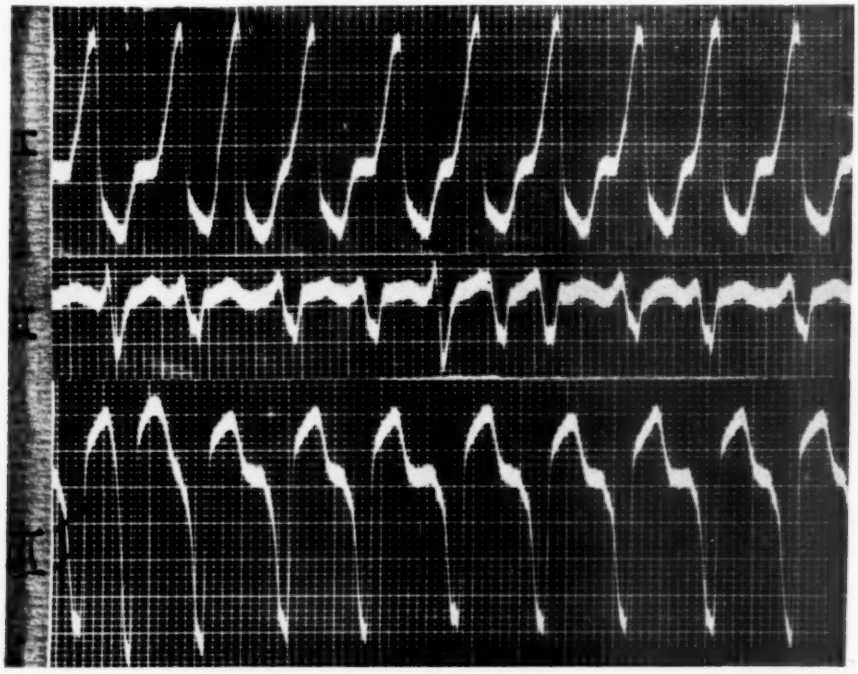

Fig. 1.—Electrocardiogram taken June 16, 1943.

change in rate or rhythm for several days. However, on June 23 the tachycardia recurred. The dose of quinidine was then increased to 24 grains a day, and, four days later, on June 26, the rhythm again became perfectly regular, with a rate of 70. The electrocardiogram (Fig. 2) on that day revealed regular sinus rhythm with a short P-R interval and aberrant QRS complex. In spite of a daily dose of 9 grains of quinidine, the tachycardia recurred once more on June 29. The tracing taken at that time was quite similar to the one taken on the day of admission. On re-examining the electrocardiograms it was found that the rhythm was

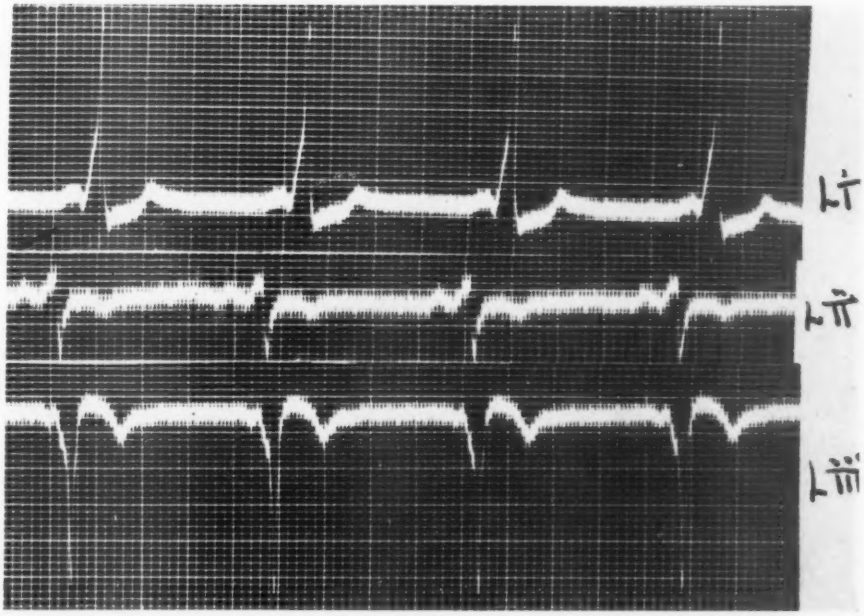

Fig. 2.—Electrocardiogram taken June 26, 1943.

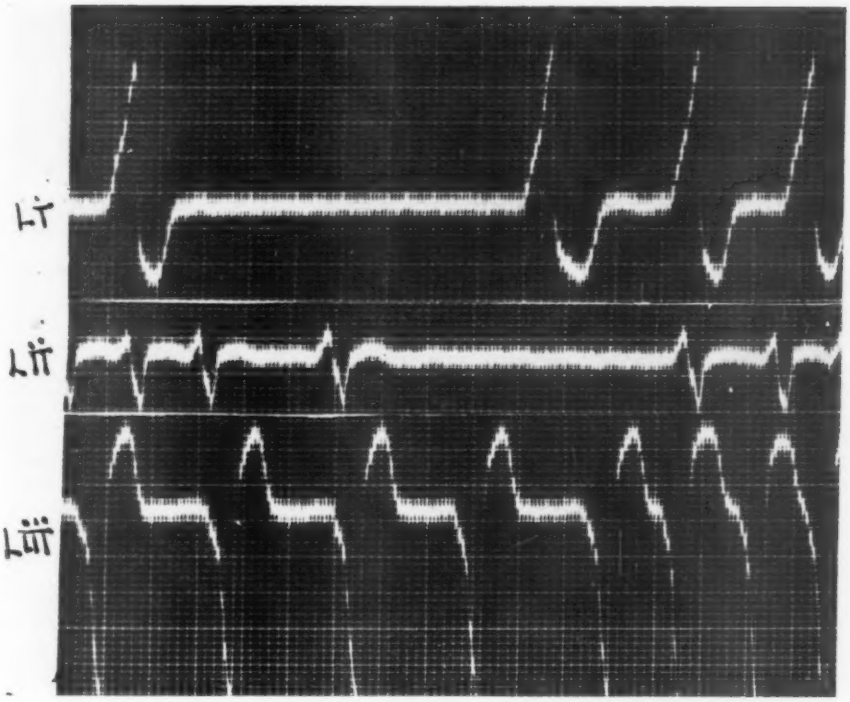

Fig. 3.—Electrocardiogram taken July 2, 1943.

really auricular fibrillation rather than ventricular tachycardia, and it was decided to digitalize the patient. Heavy doses of digitalis were administered, but, after the patient had received 39 grains of the drug in four days and was beginning to complain of nausea, a peculiar phenomenon was observed. The rhythm became even more irregular, as revealed by auscultation, and the electrocardiogram (Fig. 3) taken July 2 showed periods of ventricular asystole. It was thought that this might be due to the vagal effect of digitalis, and it was, therefore, decided (on July 3) to give the patient 20 minims of tincture of belladonna four times a day, in addition to digitalis. On July 5 the rate was found to be only about 54, with an irregular irregularity, and the electrocardiogram (Fig. 4) showed auricular fibrillation with a slow ventricular rate, but this time with a QRS which was normal in duration. In spite of continuation of the same therapy the rate returned again to what it was before the administration of belladonna, and the electrocardiogram closely resembled the one in Fig. 3. The patient complained of nausea and anorexia, and refused to eat or take any medicine. He left the hospital July 27 feeling better than he did on admission; the peripheral edema was entirely gone. He left against medical advice.

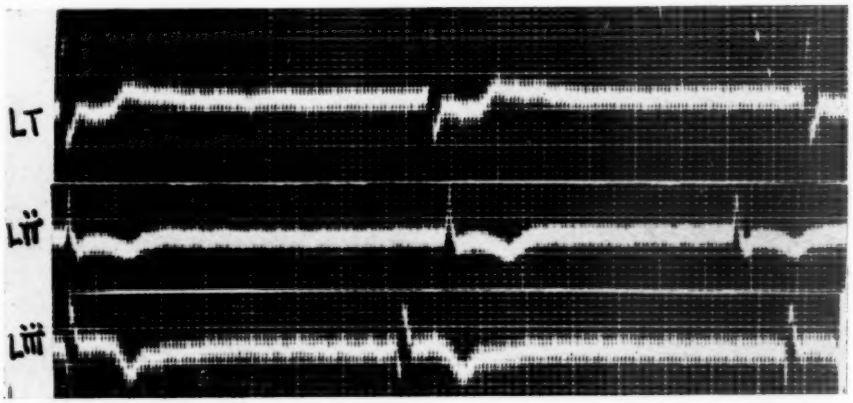

Fig. 4.—Electrocardiogram taken July 5, 1943.

The patient was readmitted Sept. 22, 1943, at which time he stated that after leaving the hospital the previous July he continued taking digitalis in doses of 1½ to 3 grains daily and felt "tolerably well" until three days before admission, when his dyspnea became more marked and he also noticed recurrence of swelling around the ankles.

It was observed that he had lost some weight, was somewhat dyspneic at rest, and had some cyanosis and slight pretibial edema. On auscultation of the heart the rhythm was found to be irregular, with an apical rate between 160 and 170 and a pulse deficit of 80. The edge of the liver could be felt about 6 finger breadths below the costal margin. The electrocardiogram was similar to the one in Fig. 1.

As it had already been observed that digitalis, even when pushed to the point of toxicity, was of no avail, it was decided to try another course of quinidine therapy. It was thought that possibly an insufficient amount of the latter drug was administered on the previous admission, and that the desired effect might be brought about with larger doses. This contention was well borne out by the subsequent course, for,

after the administration of 54 grains of quinidine within the first twenty-four-hour period, regular rhythm was restored with a rate of 70 per minute. The electrocardiogram showed sinus rhythm with a short P-R interval and an aberrant, prolonged QRS; the tracing was quite similar to the one in Fig. 2. In the next twenty-four-hour period 24 grains of quinidine were given, followed from the third day on by a maintenance dose of 3 grains four times a day for five days, and then of 3 grains three times a day. When the dose was reduced to 3 grains twice a day, extrasystoles appeared. On resumption of the three times a day schedule for quinidine, uninterrupted sinus rhythm was readily restored and maintained indefinitely.

In addition, the patient was also given digitalis, for it was believed that his cardiac decompensation was not due exclusively to the tachycardia, but that there was also organic heart disease, presumably arteriosclerotic. There ensued a quite satisfactory and well sustained improvement. The patient felt fine, the greatest transverse diameter of the heart shadow decreased 2 cm., and all symptoms and signs of decompensation disappeared, with the exception of some hepatic enlargement. The latter was thought to be due to the irreversible changes of cardiac cirrhosis. The patient was discharged from the hospital Oct. 26, 1943. At home he continued taking 3 grains of quinidine three times a day and 1½ grains of digitalis daily. He returned twice, at monthly intervals, and his condition was found to be quite satisfactory; the rhythm was perfectly regular, with a rate of between 70 and 80.

COMMENT

This case presents certain interesting and rather unusual features. The underlying organic heart disease introduces a complicating factor in the consideration of the problem. It must be conceded that there is a possibility that the arrhythmia was secondary to heart disease and was independent of the electrocardiographic anomaly of short P-R interval and long QRS. However, there are reasons to believe that the arrhythmia was definitely related to the latter. With this as a premise, the unusual features observed in this case were: (1) preservation of the abnormally long and aberrant QRS during the period of arrhythmia, and (2) the response to digitalis therapy.

It will be recalled that, in previously reported cases, return of the QRS complex to normal with the onset of tachycardia of supraventricular origin was the rule. The invariable return of the aberrant QRS to normal is explained by the hypothesis that the anomalous conduction pathway may not be sufficiently developed to be able to convey the auricular impulses when they bombard it in rapid succession.[7] The case here presented constitutes an exception to that rule, for the QRS complexes retained their abnormal length and configuration during the periods of auricular fibrillation; in fact, the duration was longer then than at other times. This raises the question as to whether the entire excitation of the ventricles did not proceed by way of an accessory tract. The less likely alternative would be that left bundle branch block (functional) was present during the tachycardia, and that only the usual pathway

was functioning. It is also interesting that, with the administration of tincture of belladonna in conjunction with digitalis for the purpose of eliminating the possible vagal effect of the latter drug, which was believed to be responsible for the short periods of complete A-V block with ventricular asystole (Fig. 3), the other possible effect of increased vagal tone, presumably responsible for the conduction of impulses through the aberrant bundle instead of the normal junctional tissue, seems to have also been abolished by belladonna, thus leading to the return of the QRS to normal (Fig. 4).

Although digitalization does not always slow the ventricular rate in all cases of auricular fibrillation, such slowing is practically the rule in cases of uncomplicated auricular fibrillation with congestive heart failure. This patient quite obviously had congestive failure, but digitalis in massive doses did not produce the expected results. Since the QRS complex during the tachycardia maintained its aberrant form, it may be concluded that, contrary to what is usual in other cases, in this instance the auricular impulses were conducted through the aberrant bundle. If this is true, the corollary would be that digitalis may be ineffective in slowing conduction through the abnormal pathway between the auricles and ventricles.

CONCLUSIONS

A consideration of the data in this case brings out two features: (1) The aberrant bundle may be able to conduct the auricular impulses during the periods of supraventricular tachycardia in cases of short P-R interval and long QRS complex, thus leading to preservation of the aberrant QRS complex during such attacks. (2) Digitalis may not exert any influence on the aberrant bundle, and the well-known effect of slowing of conduction through the normal junctional tissue by this drug may not be shared by the tissue of the abnormal pathway.

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CONGENITAL HEART DISEASE: TRICUSPID ATRESIA AND MITRAL ATRESIA ASSOCIATED WITH TRANSPOSITION OF GREAT VESSELS

Report of Two Cases

L. J. Manhoff, Jr.,* M.D., and J. S. Howe, M.D.
Richmond, Va.

ATRESIA of the tricuspid or mitral valve is a rare abnormality of the heart. Maude Abbott[1] found twenty-five cases of tricuspid atresia in her analysis of 1,000 cases of congenital cardiac disease. Six other cases have been reported since that time, including two cases by Taussig,[2] in 1936, and one each by Brown,[3] in 1936, Roberts,[4] in 1937, Gibson and Clifton,[5] in 1938, Sakaki,[6] in 1938, Harris and Farber,[7] in 1939, and Holder and Pick,[8] in 1939, making a total of thirty-three cases in the literature. In 1939 Harris and Farber collected twenty-five cases of mitral atresia, and three further cases were reported by Gibson and Clifton,[5] in 1938, Walls,[9] in 1941, and Krumbhaar,[10] in 1942, making a total of twenty-eight cases. When these lesions are associated with transposition of the great vessels they present very interesting features clinically, anatomically, and embryologically.

We wish to report two cases, one of tricuspid atresia with pulmonary atresia and transposition of the aorta, and the other of mitral atresia with complete transposition of the great vessels. A search of the literature reveals no case in which there were the same combinations of anatomic defects as either of these.

REPORT OF CASES

Case 1.—Tricuspid and pulmonary atresia, with dextroposition of aorta and associated defects.

This white female, aged 7½ months, was born by an uncomplicated delivery on Sept. 17, 1940. Shortly after birth, cyanosis became evident and was present throughout life. At the age of 7 months she developed symptoms of a cold, with progressive cough and respiratory distress, and two weeks later, on April 30, 1941, she was brought to the Pediatric Out-patient Clinic of the Medical College of Virginia. Examination revealed dyspnea, cyanosis, and clubbing of the fingers and toes. There was slight injection of the pharynx and tonsils, and a few rhonchi were heard in both lungs. Her heart was enlarged to the left, but no murmurs were heard. The erythrocyte count was 6,430,000; the hemoglobin, 113 per cent; and the leucocyte count, 10,300, with 55 per cent polymorphonuclears and 45 per cent lymphocytes. A roentgenogram of the chest showed a moderately enlarged heart, with a cardiothoracic ratio of 51 per cent and a transverse diameter of the great vessels of 3.8

From the Department of Pathology, Medical College of Virginia, Richmond.
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*At present on active duty in the Medical Corps of the Army of the United States.

centimeters. A preliminary diagnosis of congenital heart disease was made, and she was referred to the child cardiac clinic. However, the night before her appointment she developed severe respiratory distress, and the family physician was summoned. On his arrival the infant had ceased breathing, but he was able to revive her with mouth to mouth artificial respiration, and immediately sent her to the hospital emergency room. Examination there revealed the same abnormalities as before, plus extreme respiratory distress. Oxygen was administered without benefit, and she died two hours later. The clinical diagnosis was congenital heart disease with cardiac failure. Autopsy revealed, in addition to the cardiac abnormalities, pulmonary congestion and edema and passive congestion of the viscera. Microscopic examination of the heart showed fragmentation and vacuolization of the muscle fibers.

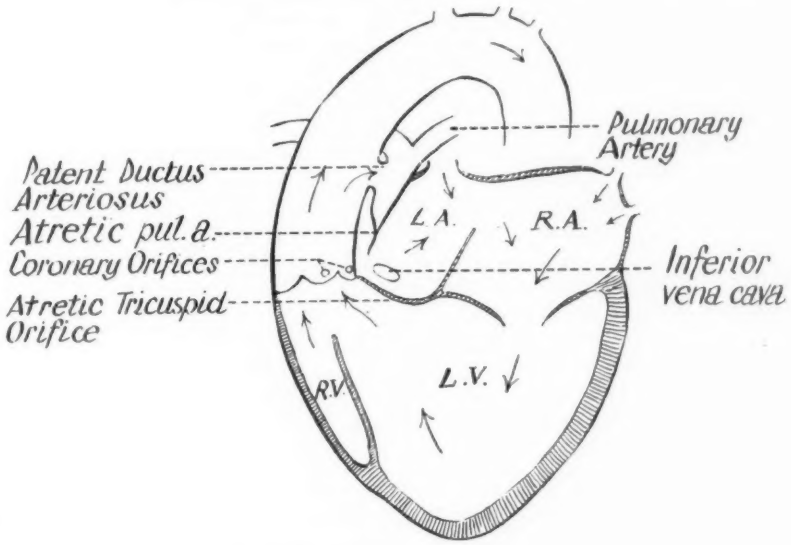

Fig. 1.

Gross Description of the Heart.—The heart weighed 45 grams and was obviously enlarged. Its apex was directed downward and to the left. The two auricles were of equal size; the right received the venae cavae and the coronary sinus, and the left received the pulmonary veins. The apex was formed by the left ventricle, which was greatly enlarged, and occupied three-fourths of the anterior surface of the heart, whereas the right ventricle was extremely small and flattened against the right side of the left ventricle.

The right auricle was normal in size and showed no appreciable hypertrophy. There was no evidence of a tricuspid valve; the floor of the auricle was completely closed by a smooth, slightly indented fibrous membrane. The only outlet of blood from the right auricle was through a defect in the upper part of the interatrial septum; this measured 1 cm. in diameter, and represented the ostium secundum of the septum primum. The septum secundum was not present. There were also numerous small perforations at the base of the septum which measured from 1 to 3 mm. in diameter. The left auricle was normal in size, and opened into the left ventricle through a normal, bicuspid mitral valve.

The left ventricle was greatly dilated and hypertrophied; its wall measured 6 mm. in thickness at the base. The interventricular septum was deflected obliquely to the right, and there was a defect in its base which measured 1 cm. in diameter. The right ventricle was small and aplastic; its cavity was little more than a narrow slit. Its wall measured 3 mm. in thickness. The aorta overrode the interventricular septal defect more to the right than to the left, so that it arose two-thirds from the right ventricle and one-third from the left ventricle. It was moderately dilated at its origin, where it measured 4 cm. in circumference. There were three aortic cusps, an anterior and a right and left posterior, with small fenestrations of each of the valve cusps. There were two coronary arteries; the left coronary arose from the sinus behind the left posterior cusp, and the right arose from behind the single anterior cusp. The aorta coursed upward normally and gave off its usual branches, including the ductus arteriosus, which was widely patent. Proximal to the ductus arteriosus the pulmonary artery became suddenly narrowed into a thin fibrous cord which did not reach the base of the heart, but disappeared 5 mm. from the right ventricle. Examination of the right ventricle failed to show any evidence of a pulmonary orifice.

Fig. 1 is a diagrammatic drawing which shows the essential features of the structure of this heart, and also demonstrates the course of blood flow through the heart. The complete anatomic diagnosis of the heart disease was as follows: (1) atresia of the tricuspid valve, (2) atresia of the pulmonary artery, (3) dextroposition of the aorta, (4) aplasia of the right ventricle, (5) hypertrophy of the left ventricle, (6) interauricular septal defect; persistent ostium secundum, (7) interventricular septal defect, (8) patent ductus arteriosus, and (9) fenestrations of aortic valve cusps.

DISCUSSION OF CASE 1

Tricuspid atresia is sometimes found as a single defect, but in the majority of cases there are many associated alterations in the architecture of the heart. Defects of the interatrial and interventricular septa, as well as hypoplasia or aplasia of the right ventricle, are almost constantly present, and transposition or pulmonary atresia is quite often associated with absence of the tricuspid valve. An interauricular communication is essential for the maintenance of blood flow, and the interventricular septal defect may be helpful in shunting blood into the pulmonary circulation in cases in which the pulmonary artery is patent. In cases in which the pulmonary artery is atretic, patency of the ductus arteriosus is necessary to bring blood into the pulmonary tree.

Cyanosis is explained by the admixture of arterial and venous blood (Lundsgaard's α factor), and by peripheral capillary stasis (Lundsgaard's D factor) which is incident to the increased back pressure on the venae cavae caused by the closure of the tricuspid orifice. The absence of murmurs in this case at first seems surprising, but may be readily explained. The only malformations in this heart which could be expected to produce a murmur were the patent ductus arteriosus and the interventricular septal defect, but since these openings were so large that they did not produce any obstruction to the blood flow, and since

there was no difference in the pressure on either side of these openings, no cardiac murmur was produced. In fact, the absence of murmurs is very helpful in the clinical diagnosis of tricuspid atresia, and Taussig[2] points out that the diagnosis can be definitely established when it is accompanied by pulmonary atresia and aplasia of the right ventricle. Persistent cyanosis with lack of cardiac murmurs narrows the field of differential diagnosis, roentgenologic studies demonstrate absence of the right ventricle, and the electrocardiogram shows left ventricular preponderance, thereby establishing the diagnosis. In addition, pulsation of the liver indicates that the foramen ovale is small and that the heart functions as a trilocular, rather than a bilocular, heart.

The mechanisms involved in the formation of this heart have many interesting aspects, some of which may be satisfactorily explained, but others we can only attempt to explain. The embryologic development of tricuspid atresia is sometimes ascribed to fetal endocarditis, especially when rudimentary and apparently fused valve leaflets are present, and when microscopic study reveals evidence of endocarditis. In this case, however, in which the valve was replaced by a smooth fibrous membrane, it seems more reasonable to consider it a true maldevelopment due to hypertrophy and resultant fusion of the fetal endocardial cushions which are the anlages of the valve leaflets. After this fusion occurred, there would be a constant flow of blood from the left to the right auricle which would prevent the closure of the interatrial defect, in this case the ostium secundum. Embryologically, the interatrial septum is first formed by the septum primum, which grows downward from the roof of the common auricle. The ostium primum is present as a defect in its base, but, as this becomes closed, the septum recedes from the roof of the auricles and the ostium secundum is formed. The septum secundum then forms along the right side of the primary septum, and a defect arises in its midportion which is known as the foramen ovale. The upper part of the septum primum acts as a flap for this foramen, and, after birth, fuses with it to form an intact interatrial septum. Therefore, if a defect is present in the midportion of the septum it should be considered a foramen ovale, if in the upper portion, the ostium secundum, and if in the lower portion, the ostium primum.

Transposition has been the most widely discussed congenital anomaly with respect to its embryologic formation, and is the most complicated and most difficult to explain. Harris and Farber[7] have reviewed the various theories, from that of Kurschner, in 1837, and Rokitansky, in 1875, to that of Spitzer in 1919 and 1921. More recently, Bremer[11] proposed a new theory based on the study of very early embryos. At present the explanations given by Spitzer are the most widely accepted and have received much support in recent literature. Harris and Farber[7] give a detailed account of Spitzer's views and report seventeen cases of transposition which support his theory. In 1941, Liebow and Mc-

Farland[12] reported a case in which there was a rudimentary right-sided aorta, thereby substantiating an important link in Spitzer's theory. Spitzer's concepts are based on studies of phylogeny as well as ontogeny, and also emphasize the importance of torsion in the development of the heart and the influence of hemodynamics in producing this torsion and affecting the development of the cardiac septa. In the normal heart there is a 180-degree clockwise rotation of the conus arteriosus. If this rotation fails to occur the aorta will arise from the right side of the heart. Dextroposition of the aorta therefore results from a partial failure of this rotation and represents the first stage of detorsion. Spitzer interprets this right-sided aorta as a persistence or reopening of the right-sided aorta of reptilian hearts, rather than as an actual migration of the aorta from the left to the right ventricle. This misplacement of the aorta infringes upon the pulmonary artery, retarding its development and producing stenosis or atresia. An accompanying rotation of the valve cusps results in two posterior cusps and one anterior cusp. The left posterior cusp, from which the left coronary arises, corresponds to the normal left anterior cusp, and the single anterior cusp, from which the right coronary arises, corresponds to the normal right anterior cusp. The proper development of the individual cardiac septa depends upon their lying along the lines of force of the blood stream, so that when the direction of the blood stream is altered there is necessarily an alteration in their formation. In the case of the overriding aorta it is usually the septum aorticum and the upper part of the interventricular septum which suffer, thereby producing a defect in the base of the interventricular septum.

CASE 2.—Mitral atresia with complete transposition of great vessels and associated defects.

This colored female infant, weighing 5 pounds 10½ ounces, was born in the St. Philip Hospital of the Medical College of Virginia on Aug. 7, 1941. She was the thirteenth child of the family, and no history was obtained of congenital defects in the previous siblings. At birth a large umbilical hernia was present and slight cyanosis was noted. On physical examination the breath sounds and heart sounds were of good quality, and immediate operation was advised. Three hours after birth the hernia was repaired without difficulty under local novocaine anesthesia, and the infant appeared to be in good condition. Six hours later the cyanosis increased and she vomited her first feedings. Fluoroscopic examination of the chest revealed a moderately enlarged heart, with widening and pulsation of the mediastinum. The impression of the radiologist was congenital anomaly of the heart and aorta. Stimulants and fluids subcutaneously were given, but respiration became more difficult and the infant died thirty-five hours after operation. The clinical diagnosis was congenital anomaly of the heart and aorta, with pulmonary atelectasis. Autopsy revealed, in addition to the cardiac abnormalities, pulmonary edema and marked chronic passive congestion of the liver and lungs.

Gross Description of the Heart.—The heart was grossly enlarged, and there was moderate dilatation of both ventricles; the right ventricle was

about twice the size of the left. There was marked dilatation of the right auricle, which was five times its normal size, whereas the left auricle was extremely small and aplastic. The right auricle received the venae cavae and the coronary sinus, and emptied into the right ventricle through a normal tricuspid valve. The left auricle was represented by a small slitlike pocket which communicated with the right auricle through a large defect in the central part of the interauricular septum. The left auricle reecived two normal-sized pulmonary veins, but did not communicate with the left ventricle. The usual location of the mitral valve was occupied by a smooth, somewhat indented fibrous membrane, with no evidence of a mitral valve or rudimentary valve leaflets. The myocardium of the left ventricle was normal in thickness, and that of the right ventricle was of the same thickness as that of the left. The two ventricles communicated through a large defect in the midportion of the interventricular septum. The aorta arose from the right ventricle and had three normal valve cusps, a single anterior cusp and a right and left posterior cusp. The coronary arteries arose from

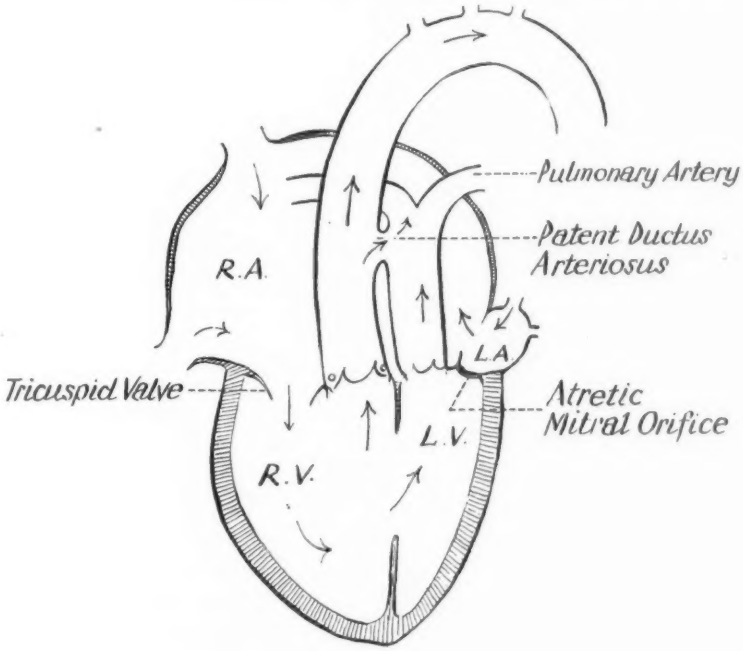

Fig. 2.

the sinuses behind the posterior cusps. The pulmonary artery arose from the left ventricle to the left of, and behind, the aorta, and it had three normal cusps. Both great vessels were of normal caliber and coursed upward in parallel. The ductus arteriosus was widely patent, and connected the aorta and pulmonary artery. Beyond the ductus arteriosus the pulmonary artery branched to supply each lung, and the aorta formed a normal left-sided arch which gave off its usual branches.

Fig. 2 represents diagrammatically the essential structural defects of this heart, and also demonstrates the probable course of circulation. The complete anatomic diagnosis of this heart was as follows: (1) atresia

of mitral valve, (2) complete transposition of the aorta and pulmonary artery, (3) aplasia of left auricle, (4) defect in midportion of interventricular septum, (5) large defect in interauricular septum (patent foramen ovale), (6) hypertrophy and dilatation of right ventricle, (7) marked dilatation of right auricle, and (8) patent ductus arteriosus.

DISCUSSION OF CASE 2

Atresia of the mitral valve is frequently associated with other structural defects of the heart, most commonly with aplasia of the left ventricle and hypoplasia of the aorta, or with some form of transposition of the great vessels, usually dextroposition of the aorta. This case is unusual in that there was complete transposition of the aorta and pulmonary artery, with an aplastic left auricle and a relatively normal-sized left ventricle. The left ventricle received a considerable volume of blood through the large interventricular septal defect, and supplied this blood to the lungs through the pulmonary artery, so that its function was sufficient to allow it to develop in spite of the closure of the mitral valve. The tremendous dilatation of the right auricle was probably due to two factors. Some dilatation was undoubtedly caused by the increased volume of blood that it carried, as it was, in effect, the only functioning auricle, and this dilatation was exaggerated by the cardiac failure.

Although this heart falls in the group with cyanosis, cyanosis was not present at birth, and congenital heart disease was not suspected until the cyanosis developed postoperatively. Fluoroscopic examination showed evidence of some anomaly of the great vessels, but, since the left ventricle was not aplastic, the mitral atresia was not suspected. The cyanosis in this case was also contributed to by the α and D factors of Lundsgaard and Van Slyke, as is true in most instances of cyanosis caused by congenital heart disease. This may have been exaggerated by interference with oxygenation of the blood in the lungs (Lundsgaard's l factor) due to the marked pulmonary congestion.

Harris and Farber[7] studied the question of transposition in association with mitral atresia, and postulated that there may be a causal relationship between the two. Of twenty-five cases of mitral atresia collected, they found that in fourteen there was also some form of transposition. In view of the rarity of both of these defects, and in view of the fact that mitral atresia does not occur in many cases of transposition, it is therefore probable that the mitral atresia in some way caused the transposition to occur. They adequately explained the usual dextroposition of the aorta by pointing out that, in accordance with Spitzer's theory, the diminished flow of blood to the left ventricle and the increased flow into the right ventricle would cause the left-sided aorta to become obliterated and the right-sided aorta to remain patent, thereby producing dextroposition or transposition of the aorta. They further state that the position and relative size of the aorta will depend

upon the time of development at which the mitral atresia takes place, and that, accordingly, four possibilities present themselves. If the atresia occurs before the obliteration of the right-sided aorta, a normal-sized or atretic dextroposed aorta will result, and if it occurs after the obliteration of the right-sided aorta, a normal-sized or atretic aorta in its normal position will be the result. All four of these varieties have been reported. In our case, however, in which there was complete transposition of both vessels, a different explanation is necessary to account for the fact that the pulmonary artery arose from the left ventricle. In studying this heart it is difficult to see how the atresia of the mitral valve could produce the complete transposition, or how the transposition could have any causal effects on the production of the atresia, for in this case neither lesion complemented the other. It therefore seems probable that the atresia and the transposition occurred independently, and that their association was merely coincidental. Transposition of the aorta and pulmonary artery would result from a complete failure of their normal 180-degree torsion, as discussed in Case 1. Mitral atresia is brought by hypertrophy of the fetal endocardial cushions, which results in their fusion and complete obliteration of the atrioventricular opening. In this connection the frequent use of the word "aplasia" seems inaccurate in referring to the obliteration of the mitral valve. This word implies a failure of growth, whereas the lesion is actually a result of overgrowth, rather than undergrowth; if there were a true aplasia or failure of growth of the valve leaflets, the result would be insufficiency of the valve.

SUMMARY

1. Thirty-three cases of tricuspid atresia and twenty-eight cases of mitral atresia have previously been reported.

2. We report one additional case of tricuspid atresia associated with transposition of the aorta and atresia of the pulmonary artery, and one additional case of mitral atresia associated with complete transposition of the great vessels. Other anomalies were present in both of these cases. No cases were found in the literature in which there were these same combinations of defects.

3. The clinical and embryologic aspects of each of these lesions are discussed.

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VEGETATIVE ENDOCARDITIS CAUSED BY HIGHER BACTERIA AND FUNGI

Review of Previous Cases and Report of Two Cases With Autopsies

Parker R. Beamer, Ph.D., M.D., Edward H. Reinhard, M.D., and Irving I. Goodof, M.D.
St. Louis, Mo.

IN MEDICAL literature there are comparatively few reports incriminating higher bacteria, yeasts, or fungi as the causal agents of vegetative endocarditis. Even more rare are the instances in which clinical diagnoses have been confirmed at autopsy. Because of the rare occurrence of such organisms in vegetative endocarditis, it is believed that a report of two additional cases will be of interest.* The causal agent was not detected in either case until post-mortem studies were completed. In the first case *Actinomyces graminis* was cultured from the heart's blood and from the vegetations on the mitral and aortic valves, and the organism was identified in histologic sections. *Histoplasma capsulatum* was identified in histologic sections from the second case, but was not obtained in cultures.

CASE REPORTS

Case 1.—F. T., a white married man, 55 years of age, entered the Barnes Hospital for the first time on June 2, 1938. His chief complaint at this time was of a large mass in the left inguinal region extending down into the scrotum; this had been present for twenty-one years.

There was no family history of hereditary disorders. The patient stated that his health had always been excellent. He had measles as a child and typhoid fever at the age of 19 years. There was no history of rheumatic fever. He denied ever having had a penile lesion or a skin eruption.

The patient's teeth had been in poor condition for many years. He had an occasional attack of abdominal pain after meals, and he thought that milk and milk products initiated this pain. His weight had been constant at 205 pounds for the preceding five years.

Born in Russia, the patient emigrated to Texas at the age of 30 years, and five years later moved to Illinois, where he remained the rest of his life. He married at the age of 37 years, and two years later a daughter was born. The patient operated a secondhand furniture business both in Russia and in this country, and for the preceding twenty-five years he had enjoyed a comfortable economic status. His diet was good and he did not use alcohol or tobacco.

From the Department of Pathology and Medicine (Dr. Reinhard), Washington University School of Medicine and the Barnes Hospital.

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*These cases were discussed in clinicopathologic conferences at the Barnes Hospital, Cases 18 and 23, J. Missouri M. A. 40: 176, 251, 1943.

The illness for which the patient first entered a hospital began in 1917, when he developed a left inguinal hernia. He wore a truss until 1934, when the hernia became incarcerated and increased in size. He entered the Barnes Hospital June 2, 1938, for repair of the hernia. At this time the only significant abnormalities were obesity, dental caries, and a large, indirect, left inguinal hernia. The hernia was repaired and the patient made an uneventful recovery.

He remained well until the fall of 1939, when he noticed a small mass in the right inguinal region. This disappeared when the patient lay down, but reappeared at intervals when he strained or coughed. At noon on Jan. 29, 1942, he had a sudden, severe pain in the right groin, accompanied by the appearance of a large mass in the right inguinal region which extended down into the scrotum. The mass could not be reduced, and the patient entered the Barnes Hospital that same day for immediate operation. At this time the general physical signs were the same as on the first admission, except that a soft blowing systolic murmur was now heard over the precordium; this murmur was heard best at the apex and was transmitted into the axilla. The blood pressure was 170/76. The hernia was repaired, and the patient was discharged from the hospital Feb. 13, 1942. On returning home he found that he weighed 180 pounds, which was 20 pounds less than his usual weight.

The patient felt well until early in April, 1942, when his right hand began to swell and a lump appeared on the dorsal aspect of the hand. At the same time he noticed red spots over this hand. He consulted a physician who diagnosed the lesion as a bruise, although the patient denied any trauma. The swelling and eruption gradually subsided spontaneously. Shortly after this he noticed increasing fatigability and developed a nonproductive cough. Toward the end of April he became aware of a heavy feeling in the left upper quadrant of the abdomen and a dry, burning sensation in his throat. He continued to lose weight, and, on his third admission to the Barnes Hospital, June 1, 1942, he weighed 171 pounds.

Upon admission to the hospital the temperature was 37° C., the pulse rate, 88, the respiratory rate, 20, and the blood pressure, 140/60. He did not appear ill. The skin was clear except for several red, elevated plaques varying in size on both hands. There was bilateral axillary and inguinal lymphadenopathy; the nodes in the axilla were 1 to 2 cm. in diameter, and were firm but not tender. The epitrochlear and cervical lymph nodes were not enlarged. It was noted again that the teeth were worn and carious, and that the pharynx was reddened. The lungs were normal. The heart was not enlarged to percussion. A faint systolic murmur was heard at the base, and a definite, blowing diastolic murmur was heard along the left sternal border and was transmitted down to the apex. The rhythm was regular. The liver and spleen were felt 4 cm. below the costal margins on deep inspiration. Bilateral herniorrhaphy scars were present. The prostate was moderately enlarged, smooth, and not tender.

At this time the erythrocyte count was 3,340,000 per cubic millimeter, the hemoglobin, 10.4 Gm. per 100 c.c., and the leucocyte count, 5,300 per cubic millimeter. The platelet count was 470,000 per cubic millimeter, and 2 per cent of the erythrocytes were reticulocytes. The Schilling differential leucocyte count showed 1 per cent basophiles, 12 per cent "stab" forms, 43 per cent polymorphonuclear neutrophiles, 33 per cent lymphocytes, and 13 per cent monocytes. A sternal bone marrow aspiration was performed and the narrow was normally cellular.

The differential count on the bone marrow was within normal limits. The urine had a specific gravity of 1.016, the albumin content was 1 plus, there was no sugar, and microscopic examination revealed only a rare leucocyte and an occasional granular cast. The Kahn reaction of the blood was negative. The stool was brown and the guaiac test was negative. The blood nonprotein nitrogen was 28 mg. per 100 cubic centimeters. The icterus index was 13. The total plasma protein value was 8.2 Gm. per 100 c.c., of which 3 Gm. represented albumin, and 5.2 Gm. represented globulin. An hippuric acid liver function test was performed, and the ratio of excreted to ingested sodium benzoate was 87 per cent. Spinal puncture revealed a clear fluid which was under a pressure of 150 mm. of water. Three lymphocytes were present per cubic millimeter of spinal fluid. The protein content was 32 mg. per 100 cubic centimeters. The Wassermann reaction was negative, but the colloidal gold curve was 2555540000.

An electrocardiogram showed left axis deviation, but was otherwise normal. A roentgenogram of the chest revealed that the cardiac silhouette and aorta were within normal limits; the hilar shadows were prominent and the lungs were normal. Anteroposterior and lateral roentgenograms of the cervical spine showed moderate hypertrophic changes about the margins of the bodies of the cervical vertebrae. A special, thick barium meal showed no abnormalities in the esophagus, stomach, or duodenum.

During the eight days the patient was in the hospital his rectal temperature ranged between 37 and 37.7° C. His general condition remained unchanged. A dermatologic consultant felt that the eruption on the hands and wrists was the iris type of erythema multiforme. An otolaryngologic consultant found nothing unusual in the nose or throat. The patient was discharged with a diagnosis of aortic insufficiency and splenomegaly, cause unknown.

The patient felt fairly well for a month after his third discharge from the hospital, and gained 10 pounds in weight. However, the heavy sensation in the left upper quadrant, the nonproductive cough, and fatigability persisted. He noticed some shortness of breath on exertion, and his ankles swelled toward the end of the day. In September he began to lose weight progressively, and fatigability increased. About this time he complained of headaches every day or two, often accompanied by dizziness. In December, his cough increased in severity until it was almost constant, and was productive of a copious amount of frothy white sputum which occasionally contained black material. Early in January, 1943, he had several mild nosebleeds. At this time the heart was markedly enlarged, and a very loud diastolic murmur was heard over the entire precordium, loudest along the left sternal border. About Jan. 10, 1943, he became somewhat restless, and his wife noted that from that time on he seemed disinterested in his surroundings, but there was no mental confusion or impairment of memory. During the night of January 16 his wife heard a noise in the bathroom and found the patient lying on the floor. He was mumbling incoherently. His breathing was noisy and he was unable to raise himself from the floor. He was taken immediately to the hospital. On subsequent questioning, the patient's wife vaguely recalled that he had been a little clumsy and had limped occasionally at intervals for a month or so.

On this, his last admission, the temperature was 37° C., the pulse rate, 140, the respiratory rate, 44, and the blood pressure, 170/10. The patient was comatose and was breathing rapidly and stertorously. He

was markedly cyanotic; the skin was pale, moist, and warm. There were no petechiae or other eruptions. The pupils were small. The eye grounds were normal except for pulsating arterioles. The neck was not stiff. The neck veins were distended and the arterial pulsations were prominent. There were coarse râles and expiratory rhonchi throughout the lungs. The left border of cardiac dullness was 12 cm. to the left of the midsternal line in the fifth intercostal space. The apical impulse was not palpable, and no thrills were felt. The cardiac sounds were obscured by the pulmonary rhonchi, and no murmur could be heard. The radial pulse was of the Corrigan type. The liver and spleen were felt 4 cm. below the costal margins. The left arm and leg were flaccid. The tendon reflexes were bilaterally hyperactive, and were more active on the left. The abdominal and cremasteric reflexes were absent. Hoffmann and Babinski reflexes were present bilaterally. There was sustained ankle clonus on the right.

The erythrocyte count was now 1,750,000 per cubic millimeter, the hemoglobin, 5.8 Gm. per 100 c.c., and the leucocyte count, 17,200 per cubic millimeters. The Schilling differential count showed 10 per cent "stab" forms, 80 per cent polymorphonuclear neutrophiles, 6 per cent lymphocytes, and 4 per cent monocytes. The urine contained 1 plus albumin, and, on microscopic examination, 1 or 2 erythrocytes and 3 or 4 casts were seen per high-power field. The Kahn reaction of the blood was negative. The blood nonprotein nitrogen was 95 mg., and the blood sugar, 138 mg., per 100 cubic centimeters. The carbon dioxide combining power of the blood was 39 volumes per 100 cubic centimeters. The icterus index was 3. On blood culture *Staphylococcus albus* was isolated, but was thought to be a contaminant. The venous pressure was 210 mm. of water.

Shortly after admission a phlebotomy was performed, and 400 c.c. of blood were withdrawn. Oxygen was administered by face mask. Aminophyllin was given intravenously and digitalis intramuscularly. After this the cyanosis diminished, the breathing was less labored, and fewer râles were heard. At this time it was noted that both arms and both legs were completely flaccid. Lumbar puncture was performed, and grossly bloody fluid was obtained at an initial pressure of 300 mm. of water.

Eight hours after admission the pulse was considerably weaker; because of this and the fact that it was now known that there was considerable nitrogen retention, the blood previously withdrawn was given intravenously, together with 500 c.c. of 5 per cent glucose solution.

During the forty-eight hours the patient was in the hospital his temperature ranged between 38 and 39° C. until a few hours before death, when it reached 40° C. The pulse rate ranged between 110 and 140 per minute, and the respirations between 40 and 52 per minute. On the second day in the hospital the urine was found to contain many erythrocytes. That evening pulmonary edema returned, the respirations became more labored and rapid, and the patient died forty-eight hours after admission.

Washington University Autopsy No. 10297 (performed by Dr. W. M. Anderson).—The surface of the body was normal except for the presence of numerous petechiae in the antecubital fossae, and the healed scars of a bilateral herniorrhaphy. All lobes of the lungs were firm, poorly aerated, and deep red in color. The spleen was large, and the pulp was red and diffluent. At the upper pole there was a decolorized infarct.

The liver was large and the lobular markings were prominent. The kidneys were enlarged, each weighing 220 grams. The surfaces were finely granular, and numerous bright red petechiae studded the cortices. The brain was slightly enlarged. In the right centrum ovale there was a blood-filled cavity which measured 5 cm. in diameter. This area of hemorrhage also involved the anterior part of the thalamus and the posterior portion of the caudate nucleus. Some destruction of the anterior part of the septum pellucidum was also present. The heart was large, and weighed 550 grams. The mitral and aortic valves were moderately thickened. On both valves there were numerous, firm, gray-white vegetations covering an area 2 by 3 cm. on the mitral valve and measuring up to 1 cm. in diameter on the aortic valve. The vegetations were largest near the free margins of the cusps of the aortic valve.

Microscopic Examination.—The aortic valve was thickened and vascularized. The vegetation was composed of a large amount of fibrin, infiltrated with polymorphonuclear leucocytes. Large and small colonies of bacteria were present. These formed dense masses, so that only a few organisms could be examined in detail (Figs. 1 and 2). They were stained variably by the Gram stain. The organisms were pleomorphic; most of them were coccoid in character, but many bacillary and filamentous forms were present. A moderate amount of granulation tissue was invading the vegetation, suggesting a subacute infection. The vegetation on the mitral valve had the same histologic appearance.

The kidneys showed the changes of chronic pyelonephritis and arteriolar nephrosclerosis. In addition, there was typical, focal, embolic glomerulonephritis in different stages of healing. Spheroidal bodies of various sizes, which were regarded as forms of Actinomyces, were present in recent lesions of this sort.

The alveoli and bronchioles of the lungs were filled with an exudate of polymorphonuclear leucocytes, large numbers of erythrocytes, and a small amount of fibrin. Many spherical, rod-shaped, and short filamentous forms of Actinomyces were present in the exudate.

In the spleen, the centers of the malpighian bodies were necrotic, and appeared as irregular masses of eosinophilic material. The endothelial cells lining the sinusoids were large and prominent. In large foci the sinusoids contained many plasma cells. Large numbers of macrophages containing hemosiderin were scattered throughout the spleen.

The wall of the cavity in the brain contained several small arteries, the walls of which showed acute inflammatory reactions. Polymorphonuclear leucocytes were present in and around the walls of these vessels.

The other organs of the body showed no relevant pathologic change. The significant pathologic changes were:

Subacute bacterial endocarditis of the aortic and mitral valves (*Actinomyces graminis*).
Focal, embolic glomerulonephritis.
Acute arteritis of small cerebral arteries.
Hemorrhage into the right cerebral hemisphere.
Bronchopneumonia of all lobes of the lungs.

Bacteriologic Studies.—At autopsy 10 c.c. of blood were removed from the right atrium and added to a tube containing 30 c.c. of tryptose-phosphate broth (Difco). In addition, 5 c.c. of blood were placed in a sterile Kolmer tube, and a loopful of blood was streaked on two blood agar plates (5 per cent rabbit's blood). Para-amino benzoic acid (5 mg. per 100 c.c.) was added to the media. Serum was collected from the

blood in the Kolmer tube and placed in a refrigerator for later studies. Cultures were incubated aerobically and anaerobically at 37° C., and observed daily for ten days. On the aerobic blood agar plate growth was first observed on the fourth day, but on subsequent transfers colonies were visible within thirty-six to forty-eight hours. Subcultures from the broth revealed growth of the same organism. Small particles of vegetations were dipped in 95 per cent ethyl alcohol and then washed in sterile physiologic salt solution. Sterile sand was added, and the vegetations were ground in a sterile mortar. The suspension thus obtained was streaked on blood agar and inoculated into tryptose-phosphate broth and incubated as already described. Colonies obtained in the aerobic plates and broth were identical with those cultured from the heart's blood. After further study the characteristics listed below were ascertained, and the organism was identified as *Actinomyces graminis* (Bostroem[1]). The patient's serum agglutinated the organism in dilutions up to 1:32, and serum from two healthy, apparently normal persons failed to cause agglutination.

1. Colonies on blood agar, forty-eight to seventy-two hours, 37° C.: round, convex, finely granular, gray-white in color, 3 to 5 mm. in diameter. Later growth was dry, umbonate, orange-brown. Tough and slightly adherent to the agar. On the sixth or seventh day colony had almost cottonlike, gray-white surface.

2. Growth in broth: ropy sediment with slight ring growth; sediment difficult to suspend by shaking.

3. Morphology of organisms (forty-eight to seventy-two hours, 37° C., blood agar): long filaments 0.6 to 0.8 μ wide, numerous long and short rods, coccoid bodies (Fig. 3). Filaments straight, wavy, and in loose groups. Conidia round or slightly elongated. Occasional branching forms. Slight tendency to formation of mycelium. No definite ray forms observed. Nonmotile. Younger growths gram positive, later becoming gram negative. Not acid-fast.

4. Physiologic reactions. Aerobic: grew poorly under reduced oxygen tension. No growth anaerobically. Would grow at room temperature. Litmus milk, peptonized in six to seven days. Gelatin, liquefied in twenty to twenty-five days. Methylene blue reduction, negative. Hydrogen sulfide production, negative. Action on sugar media: dextrose, lactose, sucrose, mannite not fermented; slight acid production in maltose.

5. Pathogenicity for animals: Intraperitoneal injection of 0.5 c.c. of broth culture produced peritonitis in guinea pigs and mice in forty-eight to seventy-two hours. Subcutaneous injections in mice and guinea pigs produced no illness or lesions. Intravenous inoculation of large doses into rabbits produced bacteremia and death in four to five days; small doses (0.2 to 0.3 c.c. of broth culture) caused no illness or lesions in animals autopsied after eight weeks of observation.

Actinomyces graminis is one of the rarer forms of this genus, but was described as a causal agent of human actinomycosis in 1891,[1] and on a few occasions since then. This is the first reported instance in which it caused vegetative endocarditis.

CASE 2.—M. G., a white man, 54 years of age, was admitted to the Barnes Hospital May 5, 1938. His complaints were of chills and fever, headaches, weight loss, and increasing weakness for five months.

The family history was irrelevant. The patient was born in Hungary. At the age of 14 years he became a baker and followed this occupation throughout the remainder of his life. He had been married twice and

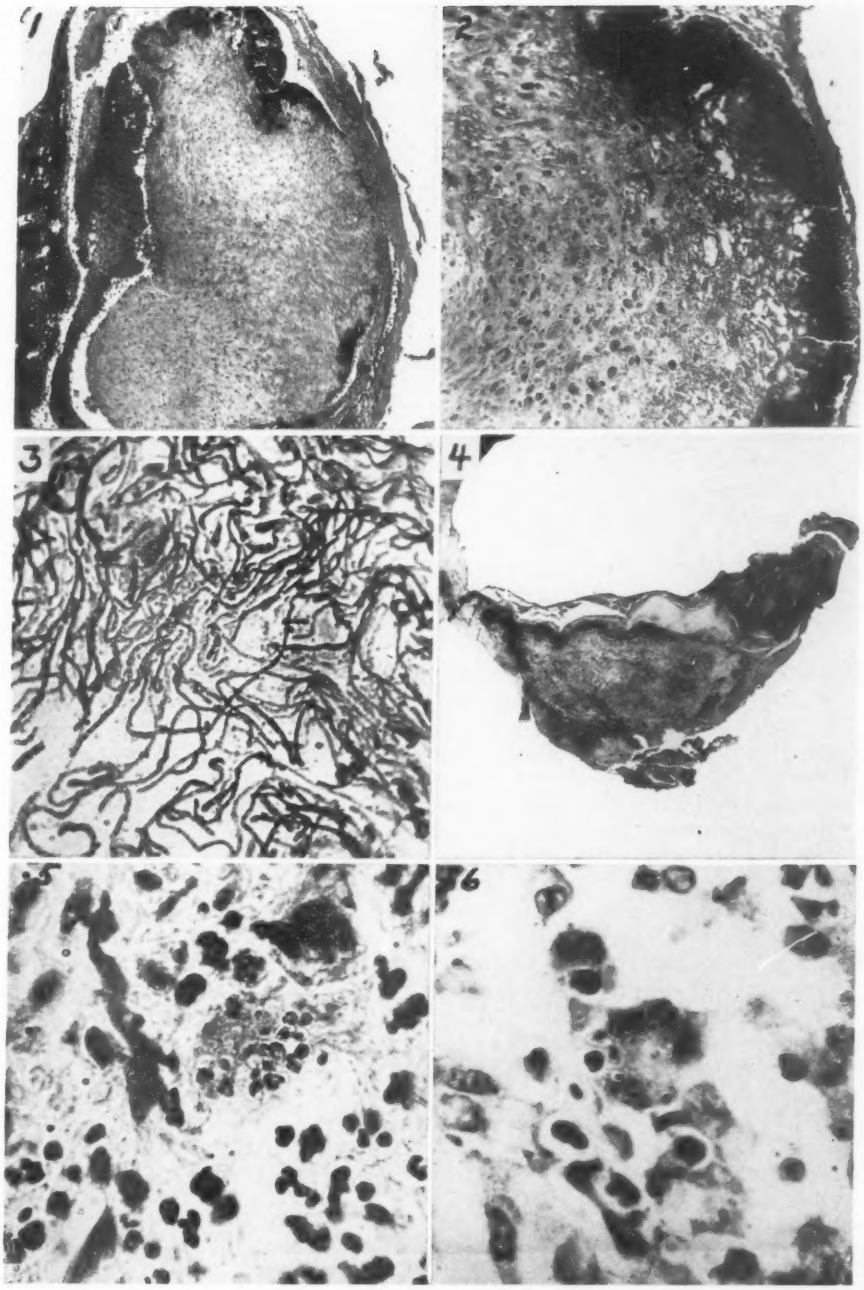

Fig. 1.—Section of vegetation (Case 1) from the aortic valve, showing dense masses of organisms surrounding granulation tissue (×30).

Fig. 2.—Section of vegetation shown in Fig. 1 under higher power (×470).

Fig. 3.—Photomicrograph of preparation (Gram stain) from forty-eight-hour culture of *Actinomyces graminis* on blood agar. Numerous filamentous, bacillary, and coccoid forms are present. Occasional branching is observed (×870).

Fig. 4.—Section of aortic valve and vegetation (Case 2), showing marked thickening of the valve (×7.5).

Fig. 5.—Higher power view of granulomatous lesion in the aortic valve (Case 2), showing several cells of *Histoplasma capsulatum* in a macrophage (×1,100).

Fig. 6—Granulomatous focus in the kidney (Case 2), showing a giant cell containing yeastlike cells, *Histoplasma capsulatum* (×1,100).

had two daughters by his first wife, whom he later divorced. During the first World War he traveled with army troops as a cook until he became a victim of "shell shock." Thereafter, he had amnesia regarding his army experiences. In 1922 he came to St. Louis, where he lived the remainder of his life.

Other than "shell shock," the only significant illness occurred at the age of 40 years, when the patient suddenly fainted and a short time later passed a copious, black stool. There were no other gastrointestinal symptoms and he continued work without interruption or recurrence of such attacks. There was no history of rheumatic fever, a penile sore, or a skin eruption of any sort.

The systemic review revealed that he had had frequent headaches for three or four years previous to admission to the hospital. His wife stated that frequently during these years he had shaking movements of the lower extremities during sleep.

The present illness began five months before admission to the hospital, when the patient became weak and drowsy. This was followed by the onset of chills, fever, and profuse sweating. His physician made a diagnosis of "grippe," and the patient remained in bed for a week. He then resumed work, but his symptoms returned and progressed. A few weeks later the patient was told by another physician that he had undulant fever. Blood tests were made, and he was told that he had syphilis as well as undulant fever. The patient was treated with tablets by mouth and almost daily intramuscular injections, but general malaise, weakness, and profuse sweating became more pronounced. He continued to have chills and fever and gradually became somewhat drowsy. Loss of appetite was progressive, and his weight decreased from 153 to 123 pounds in five months.

Upon admission, the temperature was 38.2° C., the pulse rate, 90, the respiratory rate, 20, and the blood pressure, 120/80. The patient appeared chronically ill and had obviously lost weight. He was drowsy, but conscious and well oriented. The skin was moist. The epitrochlear lymph nodes were moderately enlarged; no other nodes were palpable. The pupils were contracted. They reacted in accommodation but not to light. The mouth was edentulous. The tonsils were large, with caseous material in the crypts. There was a fine fibrillary tremor of the tongue. Chest expansion was poor, and the diaphragm moved but little to percussion. The heart was moderately enlarged. The rhythm was regular, and the sounds were of good quality. At the aortic area the second sound was loud, and there was a systolic murmur. The lungs were normal except for a few cracking basal râles which did not disappear on coughing. The abdomen was flat and relaxed. The liver was felt at the costal margin; the spleen and kidneys were not palpable. The tendon reflexes were hyperactive except for the left ankle jerk, which was barely obtainable. Sustained ankle clonus was present on the right. In the Romberg position there was slight swaying.

The hemoglobin was 82 per cent; the erythrocytes numbered 4,270,000, and the leucocytes, 4,000 per cubic millimeter. The Schilling differential count showed 14 per cent "stab" forms, 47 per cent polymorphonuclear leucocytes, 35 per cent lymphocytes, and 4 per cent monocytes. On another occasion 10 per cent of the leucocytes were monocytes. Urinalysis was negative except for 1 plus albumin. The blood Kahn and Wassermann reactions were strongly positive. Serum agglutination tests with typhoid and Brucella organisms were negative. Three routine blood cultures showed no growth. The blood sugar level was 86 mg., the urea nitrogen, 17 mg., the calcium, 8.7 mg., the phosphorus, 3.3 mg., and the

phosphatase, 4 Bodansky units per 100 cubic centimeters. The total plasma protein value was 7.8 Gm. per 100 c.c., of which 2.6 Gm. was albumin, and 5.2 Gm., globulin. Both the Takata-Ara and formol-gel tests were strongly positive. The stool was guaiac positive. The spinal fluid was clear; it contained 3 cells per c.mm. and 88 mg. of protein per 100 cubic centimeters. The spinal fluid Wassermann reaction was positive, and the colloidal gold curve was 5555555553. Brucellin and tuberculin skin tests were negative. The sternal bone marrow contained 6.5 per cent plasma cells, but was otherwise normal.

An electrocardiogram showed only left axis deviation. Roentgenographic examination of the chest revealed cardiac enlargement, widening of the superior vena cava, and infiltration of the right lower lung field. Lipiodol bronchograms were made, and there was no evidence of bronchiectasis. A posteroanterior roentgenkymogram of the heart indicated that the movements of the left ventricle were small in amplitude. Bronchoscopic examination revealed general hyperemia of the bronchial mucosa.

During the eleven weeks the patient was in the hospital he ran a continuous, high, spiking fever. He was given quinine for two days, and then atabrine for five days without effect on the fever or symptoms. He received 1.2 Gm. of sulfanilamide four times daily for four days; several weeks later this drug was administered again for eight days and there was no effect in either instance. The patient continued to have chills occasionally and was drowsy most of the time. During the fifth week in the hospital, basal râles, enlargement of the liver, and edema of the ankles were noted. He was digitalized without much improvement. During the few weeks before death he became more and more drowsy, and the blood urea nitrogen rose steadily to a level of 117 mg. per 100 cubic centimeters. Albumin, casts, and erythrocytes were found in the urine in increasing amounts. There was a persistent leucopenia; the leucocyte count ranged between 3,500 and 7,100 per cubic millimeter, and the differential count at all times showed a considerable increase in the percentage of young myeloid forms. The patient died in coma on the seventy-seventh hospital day.

Washington University Autopsy No. 7605 (performed by Dr. A. Mueller).—The body was that of a well-developed, poorly nourished white man. The external appearance was normal. The serous cavities contained no abnormal amount of fluid. The heart was normal externally. The aortic valve was thickened throughout, and one cusp was covered by a friable vegetation which involved both the ventricular and aortic surfaces. This vegetation measured about 1 cm. in diameter. A small, similar vegetation was present on another cusp of the aortic valve. The other valves were normal. The ascending aorta was widened and wrinkled. Section of its wall revealed degeneration of the media in many areas. The lungs were moist, and frothy fluid was easily expressed from the cut surface. There were fine, fragile adhesions in the right pleural cavity. No areas of consolidation were present in the lungs. The spleen was large, and weighed 390 grams. It contained numerous infarcts of varying ages. The kidneys were large, and weighed 240 and 230 grams, respectively. The surfaces were smooth, and prominent vessels were observed. The cortex and medulla of each were somewhat thickened. A vessel containing a thrombus was present near the pelvis of the left kidney. The brain was softer than usual, but was otherwise normal. No other organs showed any relevant pathologic changes.

Microscopic Examination.—The aortic valve contained a marked increase in fibrous tissue. There were many areas of calcification. Near

the surface, where the vegetation was, there was a large amount of granulation tissue. The vegetation consisted of a moderate amount of fibrin, with a cellular reaction composed of polymorphonuclear leucocytes, lymphocytes, and plasma cells (Fig. 4). No bacteria were visible in the vegetation. In the valve beneath the vegetation, there were areas of necrosis of various sizes, with necrotic cellular debris in the centers, and peripheral zones of lymphocytes, plasma cells, and macrophages. In some of these foci, macrophages were seen to contain minute spherical bodies composed of a basophilic central portion, with a clear, nonstaining peripheral halo (Fig. 5). These organisms had the morphologic characteristics of *Histoplasma capsulatum*. The kidneys, liver, spleen, pancreas, and brain presented numerous granulomatous areas of necrosis. These consisted of a central area of necrosis, surrounded by large epithelioid cells, one or more giant cells of the Langhans type, and a peripheral zone of lymphocytes and large numbers of plasma cells. These foci were scattered throughout the organs mentioned, with no specific predilection as to site. The lesions were most abundant in the kidneys and spleen, and were less frequent in the liver, pancreas, and brain. In some granulomatous foci, organisms identical with those in the valve were present (Fig. 6). In the kidneys, occasional glomeruli were partially destroyed by thrombi which involved parts of the capillary loops.

Summary of the significant pathologic changes:

Histoplasmosis involving the cusps of the aortic valve, kidneys, spleen, liver, and brain.
Thrombi in small arteries and veins of spleen, kidney, and intestinal wall.
Infarcts of the spleen.
Bronchopneumonia of the lower lobes of the lungs.
Syphilitic aortitis and aortic valvulitis.

REVIEW OF LITERATURE AND DISCUSSION

In recent years an increasing number of reports have appeared concerning patients with vegetative endocarditis caused by higher bacteria, yeasts, or fungi. For example, the recording of several cases of Candida (Monilia) endocarditis[2-6] in three years has aroused renewed interest in a mycotic infection which is known to be frequent and widespread. Furthermore, there are several reports which describe Actinomyces,[8-10] Erysipelothrix,[11, 12, 23, 24] and Leptothrix[13] as the causal agents of vegetative endocarditis, and recently a case caused by *Histoplasma capsulatum* was reported.[14]

In a statistical survey of actinomycosis in the United States, Sanford and Voelker[16] reviewed 670 cases, but found no instance in which the heart was involved. However, such involvement was observed by workers[17-20] in other countries, and later by Kasper and Pinner[21] in this country. In each of these instances, however, lesions were found in the myocardium but not on the valves. Dean[7] and Harbitz and Gröndahl[19] described two cases in which endocardial lesions were present as a result of direct extension from a focus in the myocardium.

Alestra and Girolami[8] were the first to report a case of vegetative endocarditis in which Actinomyces (Nocardia, species not ascertained) were

cultured from the blood during life, and confirmed their diagnosis by demonstrating the organisms in histologic sections and in cultures from the vegetation after death. They also studied another case of endocarditis in which Actinomyces (Nocardia, species not ascertained) were cultured from the blood during life. This patient, however, apparently recovered under therapy with an iodine compound ("Septojod"). The second authentic case of actinomycotic endocarditis was that reported by Uhr,[10] in which the causal agent, *Actinomyces bovis*, was isolated from the blood during life and its causal relation confirmed at autopsy. No other proved examples of actinomycotic endocarditis were found in the literature. Freeman[9] reported a case, diagnosed clinically as bacterial endocarditis, in which "an unusual bacillus" was isolated from the blood on three successive occasions. The organism was tentatively placed in the order Actinomycetales, but was not definitely identified. The patient died at home after a typical clinical course of subacute bacterial endocarditis, and no autopsy was performed.

Russell and Lamb[11] and Klauder, Kramer, and Nicholas[12] reported endocarditis in two cases of septicemia caused by *Erysipelothrix rhusopathiae;* this was confirmed by histologic and post-mortem bacteriologic studies. This organism is related, at least morphologically and physiologically, to Actinomyces. Three additional instances of this disease are reported in other papers, but, in two,[23] there was no bacteriologic confirmation of the histologic diagnosis, and, in the other,[24] no autopsy was performed.

Another interesting example of vegetative endocarditis caused by higher bacteria is that reported by Jervell[13] in a young man who died eight weeks after the onset of symptoms typical of vegetative endocarditis. Cultures of the blood during life and after death revealed the presence of Leptothrix, which was also cultured from the vegetations.

Histoplasmosis, a subacute or chronic, highly fatal, infectious disease caused by an intracellular yeastlike organism, occurs at all ages and in both sexes. Depending on the dominant clinical picture, the disease may be classified into several types, for example, generalized, pulmonary, intestinal, naso-oral, cutaneous, and joint types.[22] Although the infection was first described in 1906, and the reported cases number over fifty, Broders, Dochat, Herrell, and Vaughn[14] recently published the first paper describing vegetative endocarditis in association with a generalized infection by *Histoplasma capsulatum*. Moreover, in a paper now in preparation, Parsons[15] is citing at least two additional cases. Perhaps on re-examination of sections in various laboratories other instances will be discovered.*

During the past three years, six cases of endocarditis were described in which *Candida parakrusei* or *guillermondi* was the causal agent. All but one of these occurred in drug addicts. These patients presented signs and symptoms which led to the diagnosis of bacterial endocarditis,

*It is of interest that in the case reported in this paper the diagnosis was not made until Dr. M. G. Smith re-examined the sections at a later date.

and in most of them the organism was cultured from the blood during life and its causal relation confirmed by post-mortem mycologic and histologic studies. However, in one case[2] ante-mortem blood cultures yielded no growth, and, although the yeastlike organisms were observed in microscopic sections, post-mortem mycologic studies were not completed. Consequently, an accurate identification of the causal agent was not made. In the cases observed at autopsy the vegetations were engrafted upon already damaged valves, most frequently on the aortic.

The clinical diagnosis of vegetative endocarditis is not particularly difficult, even though the causal agent may not be one of the more common, and frequently recognized, true bacteria. A review of cases already reported reveals that there have been ten instances, confirmed at autopsy, in which a higher bacterium, a yeast, or a fungus was the causal agent. In all ten of these the diagnosis was based clinically on important signs and symptoms characteristic of vegetative endocarditis. Positive blood cultures were obtained in eight cases during life. The two remaining, in which no growth was obtained, were diagnosed after death as vegetative endocarditis caused by a yeast and by *Histoplasma capsulatum*.

Several factors influence the degree of success with which conclusive, positive cultures are obtained from blood and tissues. Of course, it is necessary to provide satisfactory nutritional substances and environmental conditions for the growth of the microorganisms. This frequently involves special media, containing additional nutritive substances, and modified atmospheric conditions, such as reduced oxygen tension and strictly anaerobic containers. However, the factor which is probably overlooked most frequently is the period of incubation. Several microorganisms, for example, certain higher bacteria, yeasts, and fungi, although they can develop on ordinary blood agar or carbohydrate media, do not "grow out" as rapidly as the more commonly encountered, true bacteria. Specifically, one may mention *Histoplasma capsulatum* as an example. This organism will develop on blood agar or plain carbohydrate media, but various reports indicate that an incubation period of twelve or more days may be necessary. In other instances, this organism has been observed on blood agar plates as early as the fourth to sixth day of incubation. Another example is the Actinomyces, which frequently require four or five days to produce visible growth. Consequently, when a clinical diagnosis of bacterial endocarditis is made, and blood cultures fail to show the usual organisms encountered in this condition, attention should be directed to the possibility that another causal agent is present. The routine technique must be modified sufficiently for successful culture and detection of less common microorganisms.

The natural habitat of many higher bacteria, yeasts, and fungi is widespread. Frequently, laboratory workers are not familiar with pertinent facts about such microorganisms, or, in other instances, may recognize

the forms but tend to consider them as contaminants. As Pasternack[5] has emphasized, cultures showing molds or yeasts are frequently discarded. Even after repeated culture, their presence often is attributed to a defect in technique. Recent reports of human infection caused by such microorganisms indicate that they may be more common as causal agents than was previously supposed.

Although the series of cases of vegetative endocarditis caused by higher bacteria, yeasts, or fungi is small, certain interesting facts are noted. There were ten cases[2, 3, 5, 6, 8, 10-14] with sufficient clinical data and autopsy studies to make comparisons with the two reported in this paper. Of the twelve cases, four were caused by Candida (Monilia), three by Actinomyces, two by *Erysipelothrix rhusopathiae,* two by *Histoplasma capsulatum,* and one by Leptothrix. Eleven of the patients were men, ten of whom were 35 years of age or over. In only two instances did the disease run a clinical course of less than two months; the average in the twelve cases was seven months. It is interesting that in the two cases of histoplasmosis there was a relative leucopenia, varying between 4,000 and 7,000, in contrast to the mild or moderate leucocytosis observed in the others. Of interest, also, is the elevation of serum proteins in both cases reported in this paper, with hyperglobulinemia as high as 5.2 Gm. per 100 cubic centimeters. In our case of histoplasmosis, this was attributed to syphilis, but it may be that the hyperglobulinemia was related to the primary infection in both instances. No serum protein determinations were recorded in the ten cases reviewed from the literature.

Autopsy studies reveal that vegetations caused by Candida (Monilia), two of the Actinomyces, the Leptothrix, and both strains of Histoplasma were engrafted upon valves showing sclerosis and calcification, chronic endocarditis, or syphilitic valvulitis. However, one strain of *Actinomyces bovis*[10] and both strains of Erysipelothrix attacked normal valves. Of the twelve cases under consideration, the aortic and mitral valves were involved in four, the aortic alone in five, the mitral alone in two, and the pulmonic in one case.

SUMMARY

1. Two cases of vegetative endocarditis are reported; in one, *Actinomyces graminis* was the cause, and, in the other, *Histoplasma capsulatum.*

2. Ten previously reported cases of vegetative endocarditis caused by higher bacteria, yeasts, or fungi [Candida (Monilia), Actinomyces, Leptothrix, Erysipelothrix and Histoplasma] are reviewed briefly and compared with the present cases.

3. From a study of twelve cases with autopsies, the following points may be of assistance in differentiating between vegetative endocarditis caused by bacteria and that caused by these higher forms:

(a) Greater incidence in men.

(b) Most patients were over 35 years of age.

(c) The serum proteins in the present cases were elevated, with reversal of the albumin-globulin ratio (in the other cases no data are available for comparison).

(d) In the presence of the usual signs and symptoms of vegetative endocarditis, negative blood cultures by routine procedures may suggest a less common causal agent.

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INFLUENCE OF AGE UPON BLOOD PRESSURE RESPONSE TO THE COLD-PRESSOR TEST

HENRY I. RUSSEK, M.D., AND BURTON L. ZOHMAN, M.D.
STATEN ISLAND, N. Y.

ESSENTIAL hypertension has been defined as a syndrome which is limited to persons with a hyperreactive vascular system.[1-14] This hyperreactive state, according to Hines and Brown, can be demonstrated even in childhood among persons destined to develop the disease. In support of this hypothesis, Hines[10] asserts that (1) hyperreaction to the cold-pressor test is found among people with normal blood pressure and is similar to the reaction observed in essential hypertension; (2) patients who were formerly hypertensive show a hyperreactive response even if their blood pressure is normal; (3) the incidence of hyperreaction in children approximates the combined incidence of hyperreaction and hypertension in adults; (4) hyperreactors with normal blood pressure generally come from families in which there is a high incidence of hypertensive cardiovascular disease; and (5) hypertension has developed in several patients whose blood pressure was once normal but who showed hyperreaction to the test.

Although these contentions strongly suggest that abnormal variability of the blood pressure is a heralding sign of subsequent hypertension, the observations of one of us (H. I. R.)[15, 16] failed to support this concept. In a study of two hundred normal seamen over the age of 40 years, it was found that the cold-pressor reaction did not remain constant throughout life, as alleged by Hines and Brown, but increased appreciably with advancing age. The augmented response, furthermore, applied not only to hyperreactors but also to hyporeactors (persons who showed a normal response, more correctly, normal reactors), which justifies the conclusion that vascular reactibility increases as a natural consequence of the aging process. From this it appeared that a hyporeactor at 40 years might become a hyperreactor at 50 or 60 years of age. Such a trend was further reflected in the rising incidence of hyperreaction with succeeding decades. Thus, the percentage of hyperreactors increased from 24.2 per cent in the 40- to 49-year group to 56.1 per cent in the 60- to 69-year group. On the other hand, if hyperreaction were in reality the prehypertensive phase of essential hypertension, the reverse thereof, namely, a falling incidence of "normal" hyperreactors, would have been observed with advancing age. The combined incidence of hyperresponse and hypertension in the elderly subjects of the series,

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moreover, greatly exceeded the incidence of hyperresponse in the school children observed by Hines.[6] Consequently, an appreciable percentage of these adult hyperreactors and/or hypertensives must have been hyporeactors as children. These considerations seemed to invalidate the view that hyperreaction is always an inherited and lifelong trait, closely correlated with a family history of hypertensive cardiovascular disease. Obviously, if this were the case, a positive history would indicate, paradoxically, a greater life expectancy, for the percentage of hyperreactors increased sharply with advancing age. Actual analysis, however, disclosed no relationship between the nature of the cold-pressor response and the family history of hypertensive disease. The results of that study, therefore, cast doubt upon the concept that hyperreaction is a precursor of sustained hypertension.

The present analysis was undertaken to explore these discordant views and to obtain additional data on normal persons. Since all previous studies of the cold-pressor response of normal persons arbitrarily accepted 145/95 as the upper limit of normal blood pressure, it seemed to us that this relatively high level may have permitted the inclusion of a variable number of hypertensive subjects with borderline pressures. Ayman[17] also expressed the view that some of the subjects studied may actually have been mild hypertensives, and advised that only cases in which there could be no doubt about normal status be selected. The follow-up studies of Hines,[12] furthermore, offered a rational method of classifying normal and abnormal pressures, and suggested to us a means of testing the validity of the theory proposed by Hines and Brown. In a survey of the blood pressure variations among clinic patients, Hines noted that the reading of 140/85 on first examination represented a critical level with respect to the possible occurrence of subsequent hypertension. Thus, the subjects whose systolic and diastolic blood pressure was originally in the upper range of normal (140 to 160 mm., systolic, and 85 to 100 mm., diastolic) manifested a high incidence of ensuing hypertension; whereas only a small number of those who originally had blood pressure levels in the lower range of normal subsequently developed the disease. According to Hines, therefore, the vasomotor response to the nervous stress of the physical examination serves as a "psychic-pressor test," and presents implications similar to those derived from the pressor effect of a standard stimulus of cold.

With these considerations in view, it was decided to adopt the critical level of 140/85 to differentiate nonhypertensive from prehypertensive subjects. It seemed possible by this means to obtain a group of "pure normals" who, if Hines' presumptions are correct, would manifest a strikingly low incidence of hyperreaction to the cold-pressor test. Accordingly, further studies of the cold-pressor response of healthy seamen were undertaken; the subjects were classified with respect to initial blood pressure readings into two groups, as follows: (1) Nonhypertensive subjects (initial blood pressure below 140/85), and (2) prehypertensive subjects (initial blood pressure 140/85 or above).

TECHNIQUE OF THE COLD-PRESSOR TEST

The procedure as outlined by Hines and Brown was followed throughout. The subjects remained recumbent in a quiet room, and blood pressure readings were taken over variable periods until a basal level was reached. The rest period was twenty to thirty minutes, and, usually, four to five readings were made. The sphygmomanometer cuff remained on the arm during the whole procedure, and, when the lowest level of blood pressure was reached, the free hand was placed in a basin of water at a temperature of 4° C. The hand was kept immersed to a level just above the wrist for sixty seconds. The blood pressure was measured at thirty and sixty seconds.

The response is recorded as the difference between the basal level and the maximum reading. Using the authors' criteria, subjects whose response exceeded 20 mm., systolic, and 15 mm., diastolic, were called hyperreactors. Those whose response did not exceed these figures were designated as hyporeactors.

RESULTS

The test was performed on three hundred fifty merchant seamen between the ages of 40 and 69 years. Data on two hundred of these subjects formed the basis of a previous report.[15] All were ambulant hospital patients who had been admitted for a variety of minor ailments unrelated to the cardiovascular system. The initial blood pressure on admission to the hospital was used to classify these patients in the manner described above. There were two hundred forty subjects in the nonhypertensive group and one hundred ten subjects in the prehypertensive group. The highest initial pressure in the study did not exceed 160/100.

In Table I the average response of the blood pressure to a standard stimulus of cold is analyzed with respect to age, initial blood pressure level, and type of response. It is seen that there was an appreciable rise with age in the average response of all subjects, whether they were hyporeactors or hyperreactors. Even when the subjects with lower levels of normal blood pressure were considered as a group, this increase in average vasoconstrictor response with advancing age was clearly evident.

Table II shows that when all subjects were considered, there was an appreciable increase in the incidence of hyperreaction with succeeding decades. The frequency rose from 34.8 per cent to 63 per cent in the age period studied. Of the entire group, 49.7 per cent were hyperre-

TABLE I

ANALYSIS OF COLD-PRESSOR RESPONSE BY AGE AND INITIAL BLOOD PRESSURE LEVEL

AGE (YRS.)	BLOOD PRESSURE 160/100 AND LESS				BLOOD PRESSURE LESS THAN 140/85			
	HYPOREACTORS		HYPERREACTORS		HYPOREACTORS		HYPERREACTORS	
	SYST.	DIAST.	SYST.	DIAST.	SYST.	DIAST.	SYST.	DIAST.
40 to 49	10.1	7.6	25.0	18.6	10.0	7.5	24.6	18.0
50 to 59	16.0	11.4	33.2	23.2	15.2	11.5	32.0	22.1
60 to 69	17.3	13.3	35.6	24.6	17.1	13.1	35.2	22.1

TABLE II

PERCENTAGE INCIDENCE OF HYPERREACTION BY AGE AND INITIAL BLOOD PRESSURE LEVEL

AGE (YRS.)	LESS THAN 140/85 (240)	140/85 TO 160/100 (110)	160/100 AND LESS (350)
40 to 49	24.7	66.7	34.8
50 to 59	42.0	70.0	52.2
60 to 69	56.7	75.8	63.0
40 to 69	40.0	70.9	49.7

actors to the cold-pressor test. When the analysis was carried further, and the two blood pressure groups were studied independently, it was found that the rising incidence of hyperreaction was particularly marked in the nonhypertensive class, in which the increase was from 24.7 per cent in the fifth decade to 56.7 per cent in the seventh decade. In the prehypertensive group, on the other hand, the incidence of hyperreaction increased more slowly with age, rising from 66.7 per cent to 75.8 per cent in the same period. Hyperreactors comprised 70.9 per cent of the prehypertensive subjects, as compared with 40 per cent of the nonhypertensive subjects.

DISCUSSION

Abnormal variability of the blood pressure is regarded by many authors as one of the outstanding characteristics of essential hypertension. In the opinion of Hines and Brown, vascular hyperreaction in persons with normal blood pressure means either a predisposition to hypertensive disease, or previous hypertension which is temporarily latent. Other observers,[18-23] similarly, have emphasized the prognostic significance of even transient elevation of the blood pressure in subjects who generally have normal levels.

Our observations strongly suggest, however, that excessive reactibility of the blood pressure may be a physiologic occurrence in the later decades of life. This conclusion is based upon the observation that the vasopressor response to a standard cold stimulus rises appreciably with advancing age. In our series, an increase in the range of reaction was noted not only among hyperreactors, as reported by Hines and Brown, but also among hyporeactors. As would be anticipated, the incidence of hyperreaction showed a corresponding rise with age, so that hyperresponse was almost twice as frequent in the seventh decade as in the fifth. These observations suggest that age exerts an important influence upon the response of the blood pressure to a standard stimulus of cold.

The tendency for a normal reaction to become "excessive" was unrelated to the initial blood pressure level, inasmuch as the hyporeactors in both blood pressure groups showed a similar increase in response with succeeding decades. The incidence of hyperreaction increased with age in the nonhypertensive group from 24.7 per cent to 56.7 per cent, and, in the prehypertensive group, from 66.7 per cent to 75.8 per cent.

Hyperreaction was found in 70.9 per cent of the subjects who were likely to develop hypertension, as compared with only 40 per cent of those who were unlikely to develop it. This difference is statistically significant, and clearly indicates that hyperresponse is more common among subjects destined to develop the disease. Nevertheless, the high incidence of vascular hyperreaction among nonhypertensive subjects makes it equally apparent that no specific correlation exists between hyperresponse and subsequent hypertension. In this regard, it should be noted that the older the group considered, the less was the disparity in incidence of hyperreaction between the respective blood pressure groups. Vascular hyperreaction, therefore, appears to arise, in later life at least, from factors related to the aging process.

From these observations it would seem that there is a progressive increase in the irritability of the vasomotor mechanism with advancing age. A similar conclusion was reached by Raab[24] in his studies of the blood pressure response to the inhalation of carbon dioxide. In reporting the pressor effect at various ages, the author stated that there is "increasing irritability of the cerebro-medullary vasoconstrictor centers" with advancing years. He attributed the rising vasopressor response to a gradual diminution in cerebral blood flow, which leads to ischemia of the nerve centers controlling vascular tonicity. Others have shown, moreover, that arteriolar sclerotic changes, associated with decreased cerebral blood flow, are common features of advancing age. Consequently, Raab's observations, employing the stimulus of carbon dioxide, are supported by our own observations, using the stimulus of cold.

It appears from this evidence that cerebral vascular ischemia develops in an increasing percentage of persons with advancing age. Whether or not such central changes and their consequences are always to be regarded as pathologic is still an unanswered question. The recent experiments of Fishback and his co-workers[25] suggest that decreased cerebral blood flow may be an important factor in the etiology of hypertension. These authors were able to produce sustained elevation of blood pressure in animals by ligating arteries supplying the head. On the other hand, it would seem from our data that cerebral ischemia, as manifested by vascular hyperreaction, is found in a significantly high percentage of older persons who never develop hypertensive disease. We have noted, in fact, that hyperresponse is not uncommon even in "hypotensive" subjects (systolic pressure 110 mm., or less) in the later decades of life. It cannot be denied, therefore, that vascular hyperreaction may be physiologic in many middle-aged and elderly subjects.

SUMMARY AND CONCLUSIONS

The cold-presser reaction of three hundred fifty male subjects over the age of 40 years was measured. A comparison was made between the response of persons with initial pressures in the upper range of normal

(prehypertensive) and that of persons with initial pressures in the lower range of normal (nonhypertensive). It was concluded that:

1. The response of the blood pressure to a standard stimulus of cold tends to increase in all subjects with advancing age.

2. The rising response appears to result from increasing irritability of the vasomotor centers, an effect of the vascular changes associated with "aging."

3. The tendency for a normal reaction to become "excessive" is reflected in the rising incidence of hyperreaction with succeeding decades.

4. There is a marked increase in the frequency of hyperreaction with advancing age among "subjects unlikely to develop hypertension," suggesting that such a response is frequently physiologic in the later decades of life.

5. Hyperreaction is more common among prehypertensive subjects than among nonhypertensive persons, but the difference in frequency between the respective groups becomes much less marked with advance of age.

6. The high incidence of hyperreaction among the nonhypertensive subjects indicates that such a response cannot be regarded as specific for potential or latent hypertension at this age.

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Clinical Reports

BUNDLE BRANCH BLOCK, WITH SPONTANEOUS REMISSION AFTER FOUR YEARS

Report of a Case

Joseph Kalett, M.D.
New Britain, Conn.

THERE have of late been increasing numbers of reports of transient, complete, bundle branch block, but all writers agree that, once established, the block will remain as a permanent feature. A careful search of the literature failed to reveal any case in which bundle branch block persisted over a period of years and disappeared spontaneously. In a personal communication, Dr. Paul White, of Boston, stated, "I have never seen or heard of a patient whose electrocardiogram returned to normal after years of constant bundle branch block." A similar communication from Dr. H. M. Marvin, of New Haven, Conn., confirmed this opinion, and both, after reviewing the electrocardiograms, suggested the desirability of reporting this case.

CASE REPORT

R. D., aged 56 years, a white man, first presented himself for examination on Sept. 13, 1938. Two years previously, while shoveling snow, the patient collapsed. He recalled no accompanying pain. Two weeks later he had another attack, this time accompanied by a moderate amount of precordial pressure which lasted about twenty-four hours. The patient was apparently told that he had "heart disease," and was advised "to avoid excitement and take things easy." Retirement from active work had been advised. His only complaint at the time of his first visit was of moderate fatigability.

Physical examination revealed a well-nourished and well-developed man who weighed 194 pounds. The pulse was regular and the rate was 86. There was moderate retinal sclerosis. The chest wall was rather thick and the thorax was emphysematous. The heart sounds were somewhat distant, but well heard. There were no murmurs. The blood pressure was 116/80. The blood Wassermann reaction and urinalysis were negative. Fluoroscopic examination showed moderate enlargement of the left ventricle and some elongation of the thoracic aorta. An electrocardiogram on Sept. 13, 1938 (Fig. 1), showed left bundle branch block. The P-R interval was 0.16 to 0.18 second. T-wave inversion was present in Lead I. The QRS interval was 0.15 second.

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From the Department of Cardiology, New Britain General Hospital.

The patient left New Britain and was not seen again until Feb. 6, 1940. At this time there was little change in the physical signs, and there were no symptoms. An electrocardiogram (Fig. 2) showed left bundle branch block exactly as before.

The patient, unfortunately, was not seen again until Oct. 3, 1942. At no time had he had any symptoms. An electrocardiogram which was taken

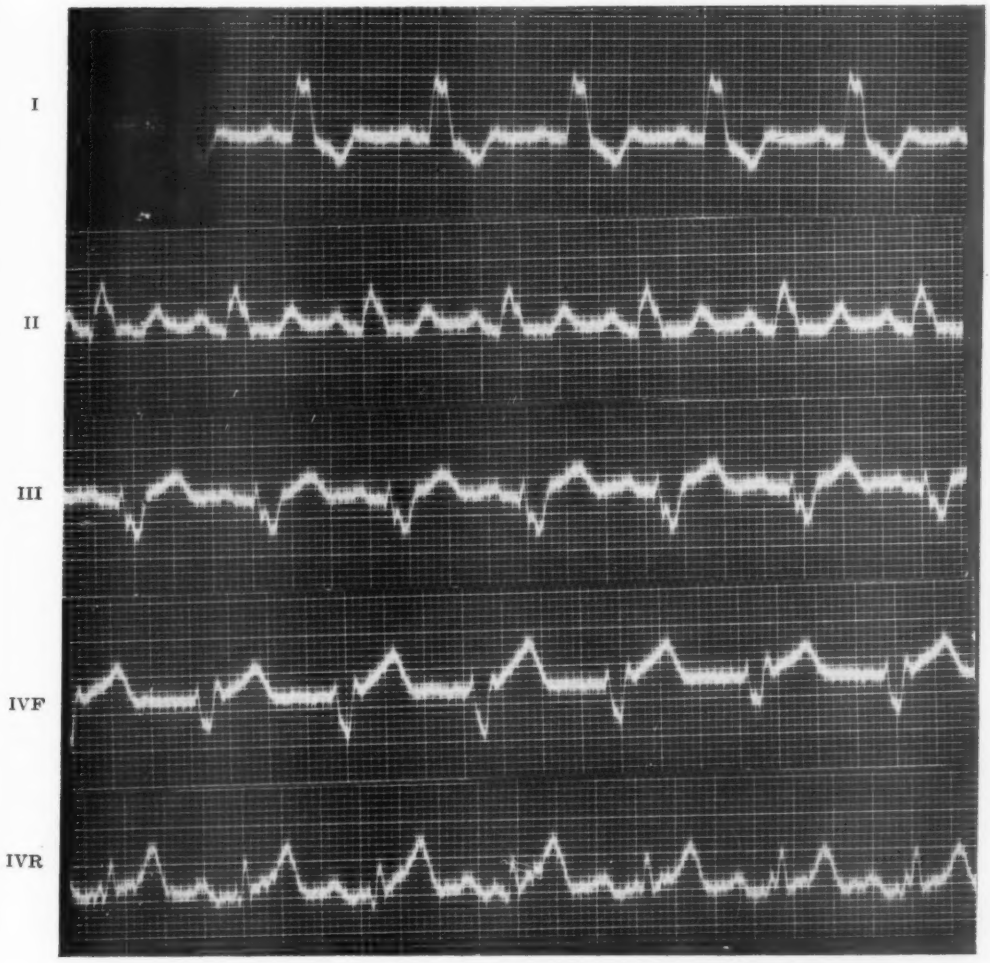

Fig. 1.—Taken Sept. 13, 1938, showing left bundle branch block.

(Fig. 3) at this time showed that the bundle branch block was not present. Another electrocardiogram was taken Oct. 27, 1942 (Fig. 4), and again June 12, 1943 (Fig. 5), and both were the same as that of Oct. 3, 1942 (Fig. 3).

DISCUSSION

In this case the left bundle branch block followed acute coronary occlusion. There have been no reported exceptions to the observation

that bundle branch block, once established in cases of organic heart disease, remains throughout life. Transient, complete, bundle branch block has been rather infrequently reported. In the series of cases reported by Kurtz,[1] bundle branch block had a duration of a few moments to ten months, but he concludes that, once established, the block persists for the remainder of the patient's life. Master, Dack,

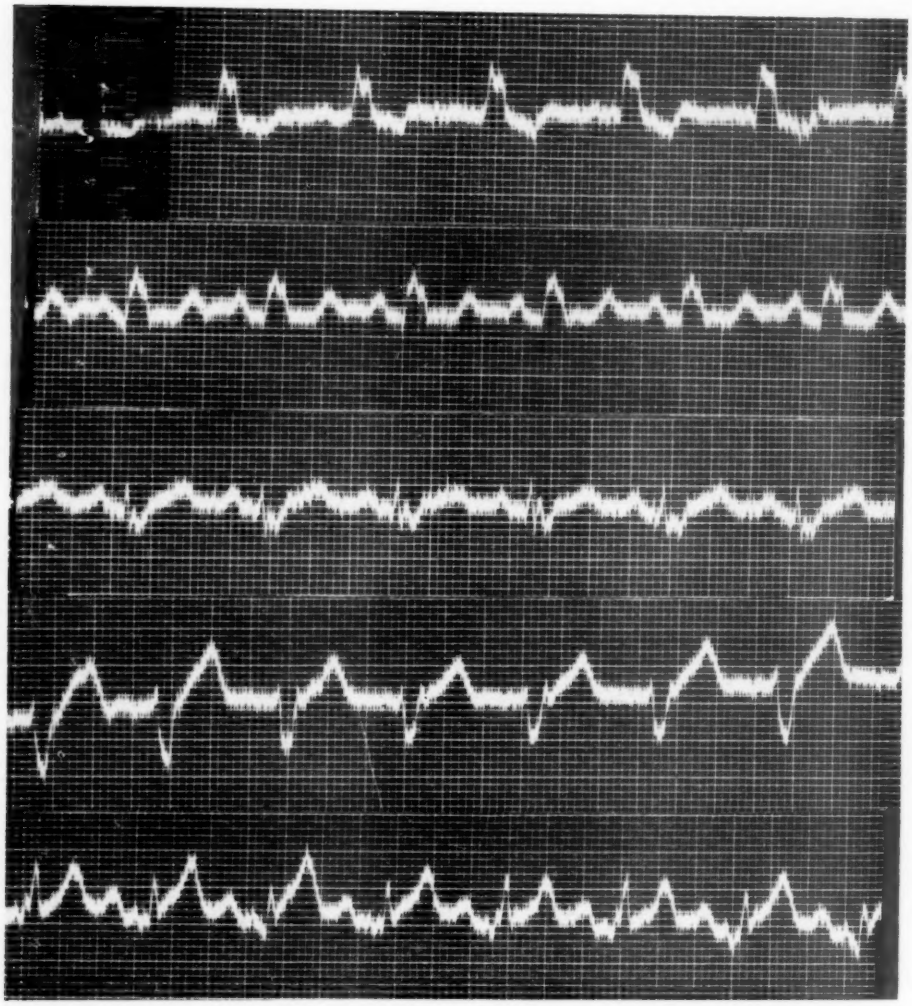

Fig. 2.—As in Fig. 1. Taken Feb. 6, 1940.

and Jaffe[2] wrote: "The conduction defect persisted in 23 patients until death. . . . In 27 patients who survived, the conduction defect was still present in records taken several months to two years later." In a single case reported by Bishop,[3] the transient, recurrent, bundle branch block lasted about six months. It later became permanent.

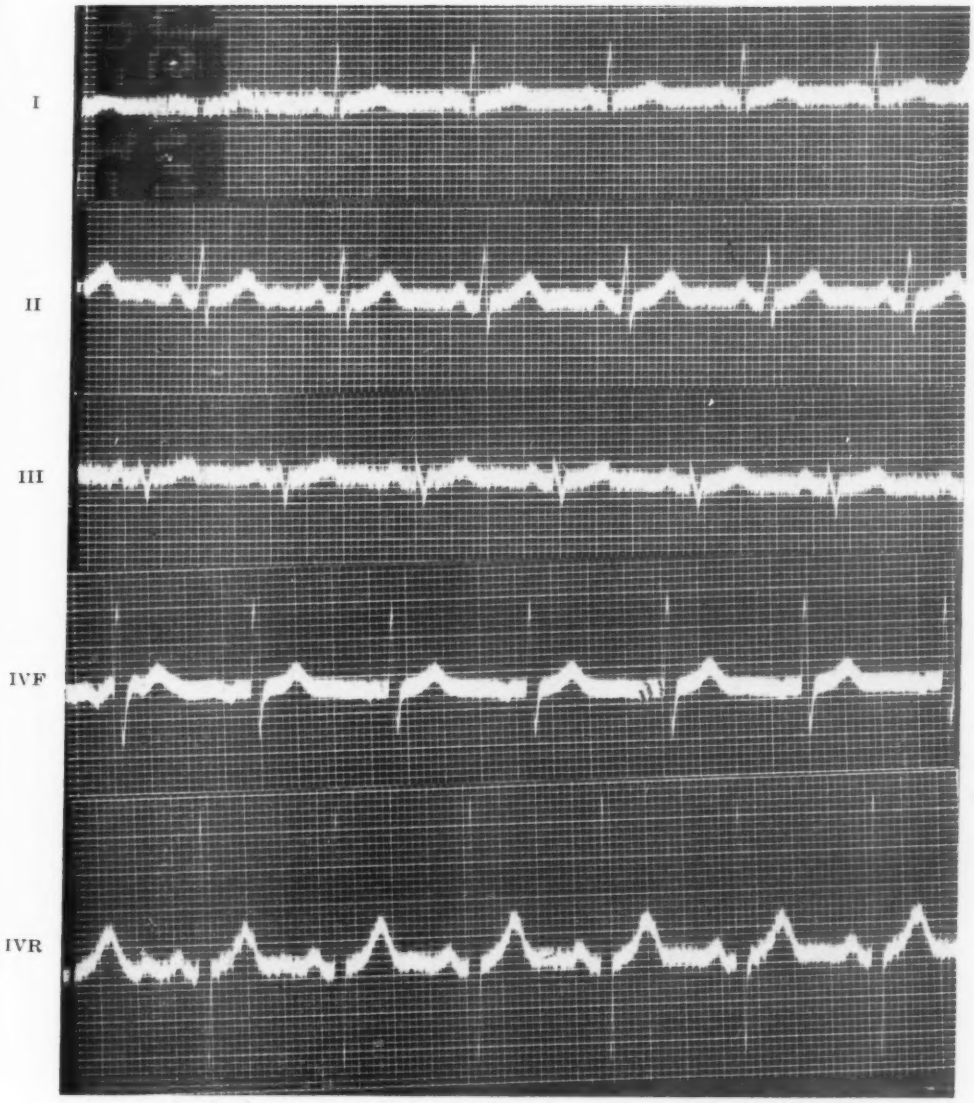

Fig. 3.—Taken Oct. 3, 1942, showing absence of block and left axis deviation.

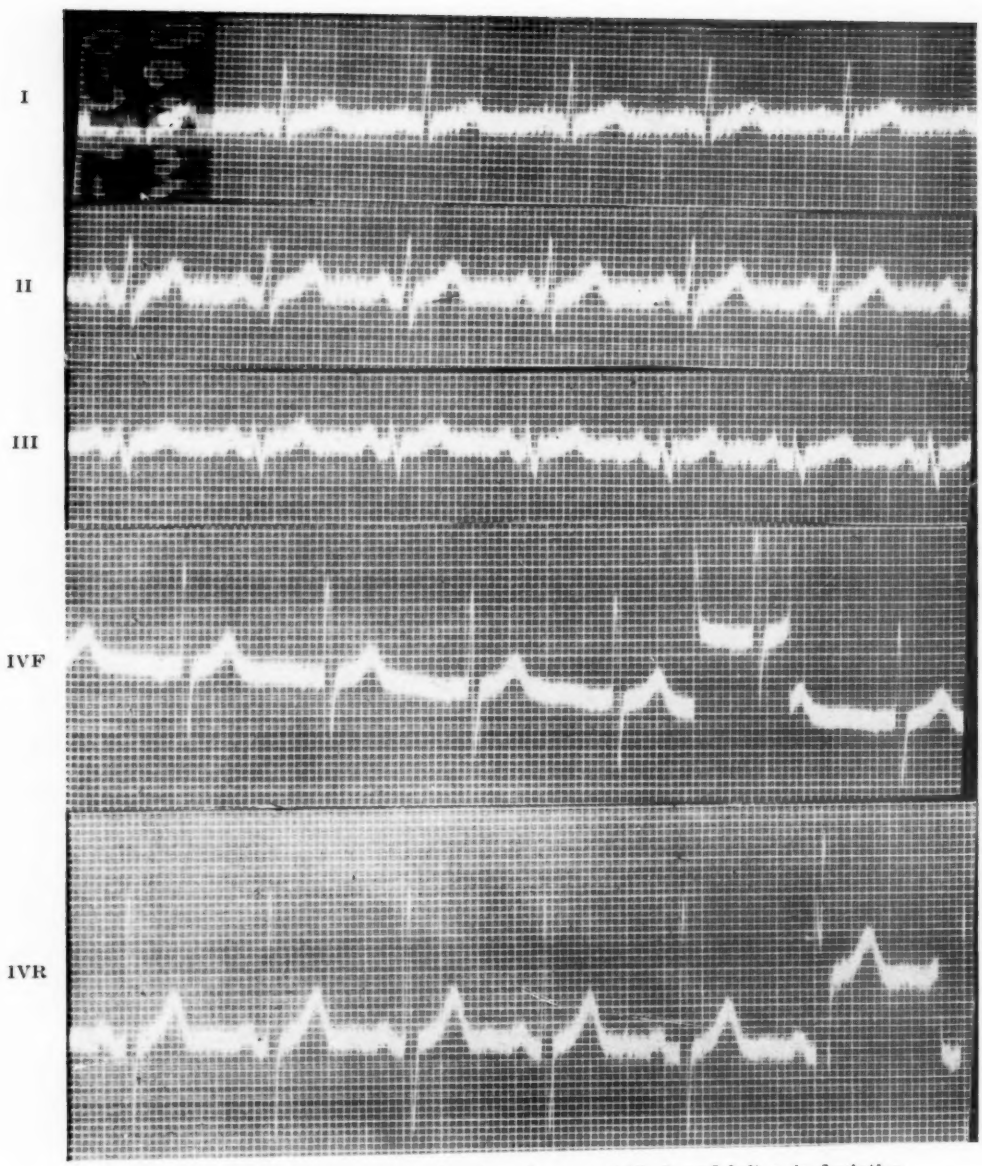

Fig. 4.—Taken Oct. 27, 1942, showing absence of block and left axis deviation.

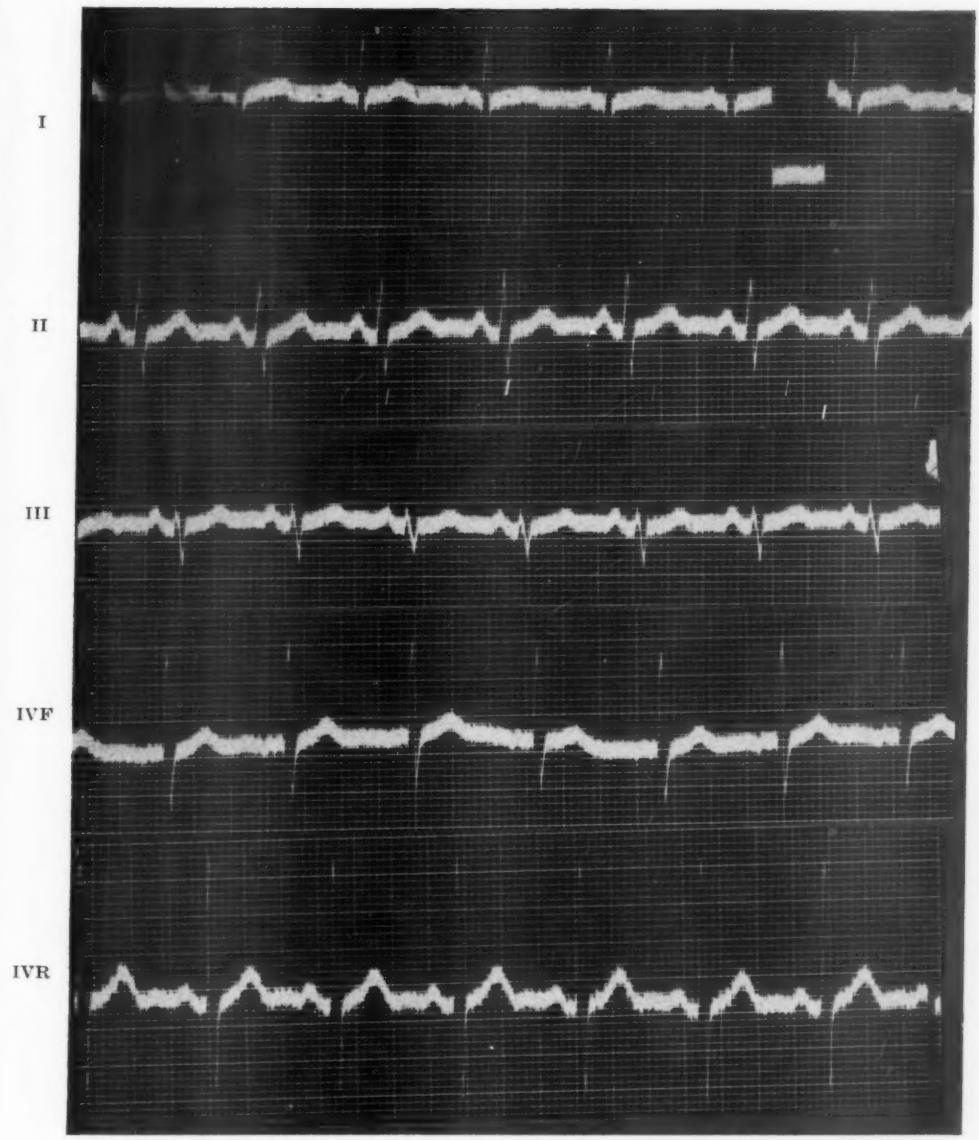

Fig. 5.—Taken June 12, 1943, showing absence of block and left axis deviation.

SUMMARY

A case of bundle branch block following coronary occlusion is presented, in which spontaneous disappearance of the block occurred after a period of about four years. No similar case of persistent block which disappeared after so long an interval has been found in the literature. The case is of particular interest because the patient remained symptom free throughout the period of observation. In the presence of the bundle branch block, and in the transition to normal QRS complexes, no variations in symptoms or physical signs were apparent. This interesting paucity of symptoms parallels the case of Willius and Anderson,[4] as well as that of Bishop.[3]

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CARDIAC HYPERTROPHY OF UNKNOWN CAUSE

Report of a Case

George H. Reifenstein, M.D., and A. Dwight Chidsey, M.D.
Syracuse, N. Y.

HYPERTROPHY of the heart occurs as a result of some physiologic or pathologic disturbance. In most instances, the mechanism is apparent. There have been, however, a group of cases of myocardial hypertrophy for which no definite cause has been demonstrated. In most of these, the hypertrophy has been associated with endocardial fibrosis and varying degrees of myocardial degeneration, and has occurred in infants and children up to 4 years of age.[1-4] Various theories have been postulated to account for the changes; these include intrauterine infection during the early days of life, "congenital weakness of the germ plasm,"[1] and allergic reaction to milk in a heart which was already damaged by infection.[2] Kugel[3] has spoken of these as cases of "non-suppurative myocardial degeneration with dilatation and hypertrophy." Similar cases have been reported in which hypertrophy and endocardial fibrosis occurred without myocardial degeneration.[1, 5]

There are few reports of obscure cardiac enlargement in older children and adults, probably because of the multiplicity of physiologic or pathologic disturbances which occur with age and might more readily account for the changes within the organ. Whittle[6] reported one case of an apparently well-developed 20-year-old student who fell from his bicycle and died within a few moments. Post-mortem examination revealed a markedly hypertrophied heart, weighing 840 grams. The valves, endocardium, and coronary arteries appeared normal. The aorta was somewhat small and delicate, and measured 16 mm. in diameter at the commencement of the descending portion. There were no other congenital anomalies. The only additional gross abnormalities were an acute tracheitis and a persisting thymus gland, weighing 30 grams. Histologic study of the heart showed swelling and loss of striation of the muscle fibers, with no foci of inflammation or necrosis. All of the other organs appeared normal. The author felt that neither the narrowed aorta nor the persistent thymus could have accounted for the marked cardiac enlargement, although the acute tracheal infection might have been responsible for the cloudy swelling of the myocardial fibers. He postulated that prolonged muscular exertion of cycling might have played an important factor.

From the Department of Pathology, Syracuse University College of Medicine.
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Kugel[3] states that he has observed two cases in adults in which the lesions were similar to those in his group of infants. Levy and Rousselot[7] reported three cases of cardiac hypertrophy of unknown origin in adults. Later,[8] one case was discarded because it could possibly have been von Gierke's disease, but eight other similar cases were added to the series. No apparent cause for the myocardial disease and enlargement could be demonstrated. There were eight males and two females, ranging in age, at death, from 26 to 66 years; symptoms of decompensation had been present from ten days to five years. In six of the cases there was some myocardial necrosis or fibrosis, and mural thrombi, with emboli to other organs, were conspicuous. Two patients had positive complement fixation tests for syphilis, although no evidence of syphilitic tissue changes could be demonstrated. In no case was there any generalized arteriolar sclerosis to indicate previous hypertension. Reisinger and Blumenthal[9] reported five similar cases, in four of which there were positive Wassermann reactions, and they considered the etiological relationship of syphilis to myocardial disease. Two other cases in adults, but without serologic or other evidence of syphilis, have been reported in the Case Records of the Massachusetts General Hospital.[10, 11]

In view of the paucity of literature concerning cardiac hypertrophy without recognized cause in older children, we record the following case.

CASE CM—5715.—An 11-year-old schoolboy was examined three hours after death. He was said to have been a normal, healthy child. At the age of 2 years a broken leg was treated without complication. He had measles and chicken pox during early childhood, but no other illnesses. His progress in school was satisfactory. He performed ordinary exercises in the gymnasium, rode a bicycle, and played with other children without any apparent difficulty. On the day of death he arose, ate breakfast, and went to school as usual. While sitting at his desk during the morning class he started to rise suddenly from his seat, cried out, and fell to the floor, striking the right frontotemporal region of his head upon a desk. He appeared comatose and cyanotic, and was dead a few minutes later.

Post-mortem Examination.—The body was that of a fairly well-nourished and well-developed white male child; height, 4 feet, 5½ inches; weight, 80 pounds. There was cyanosis of the lips and fingernails.

There was a small, linear fracture of the right temporal bone, with slight hemorrhage along the fracture line. The ventricle of the brain contained bloodtinged fluid, and there were a few punctate areas of hemorrhage in the medulla near the floor of the fourth ventricle; otherwise, the brain substance was without evident lesion. The thymus weighed 45 grams, and there were scattered punctate areas of hemorrhage beneath the capsule.

The heart weighed 430 grams, and there was marked concentric hypertrophy of the left ventricle with only slight hypertrophy of the right ventricle. None of the chambers were dilated. The myocardium appeared uniformly pale and firm, and the markings of the muscle bands

stood out distinctly. The wall of the left ventricle measured up to 3.5 cm. in thickness. There was a reduplication of the left cusp of the pulmonary valve; the fourth cusp appeared rather small, and showed some fenestration along the free margin. Otherwise, the valves and remaining endocardium were without evident lesions. The foramen ovale and ductus arteriosus were closed. The coronary ostia were normal in size and location; the vessels throughout were patent, and showed no intimal sclerosis. There was no narrowing of the aorta or of any of the great vessels arising from it.

Fig. 1.—Heart muscle; idiopathic hypertrophy showing glycogen stain with droplets (×710).

The other organs showed no noteworthy changes.

Microscopically, the brain showed some edema. There was hyperplasia of the thymus, with rather numerous polymorphonuclear leucocytes in the pulp. The liver, kidneys, lungs, and other organs appeared to be entirely without evident lesion. There were no vascular changes.

There was marked hypertrophy of the muscle fibers of the myocardium, with very slight diffuse increase in fibrous tissue between the muscle bundles. There was no vacuolization of the muscle fibers, and

no areas of degenerative change in sections stained with hematoxylin and eosin. The large and small vessels of the heart appeared normal, and there was no perivascular cellular infiltration. The endocardium and subendocardium were not thickened. Fat stains and Masson and Heidenhain stains did not contribute anything. Best carmine stains for glycogen on alcohol-fixed myocardium showed some areas with numerous, moderate to fine, red droplets, located, for the most part,

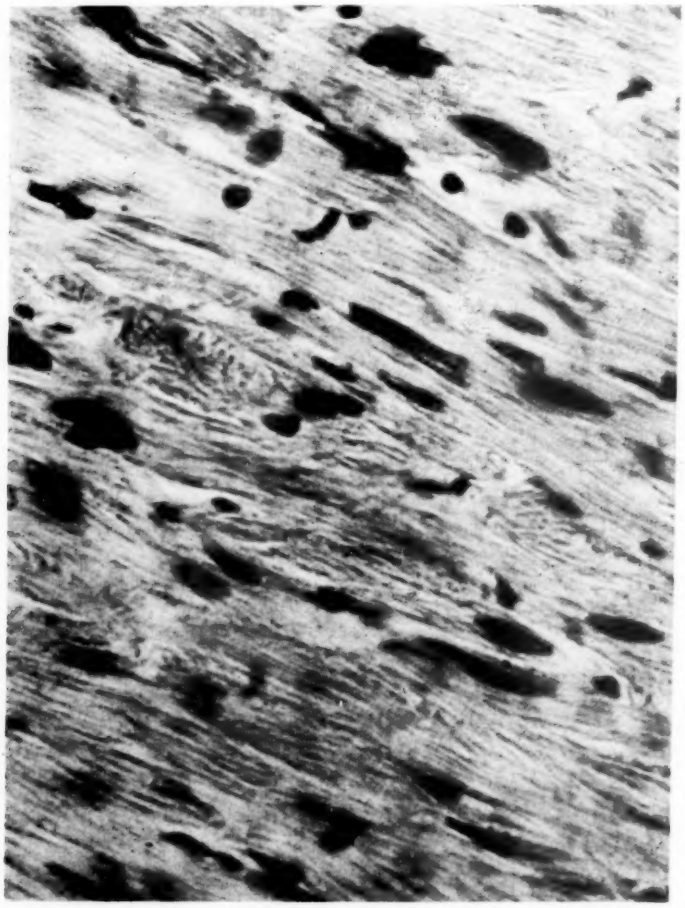

Fig. 2.—Heart muscle; idiopathic hypertrophy showing glycogen stain without droplets (×710).

within the fibers, although some were in connective tissue between the fibers. Some of these fine droplets were located transversally, like striations, across the myofibrils (Fig. 1). Other areas showed the same marked hypertrophy of the muscle bundles, but no glycogen deposits (Fig. 2). In no place did the enlargement of the muscle fibers appear to be the result of glycogen accumulation.

Quantitative analysis of the myocardial glycogen by hydrolysis and the Benedict micro method[12] showed 0.16 per cent glycogen, as contrasted with a normal of 0.07 per cent. Best carmine stains of the kid-

ney showed no evidence of glycogen. The liver did not contain an abnormally large amount of glycogen; chemical analyses of these tissues were not made.

COMMENT

It is of interest to note the clinical and gross pathologic similarities between this case and the one reported by Gardner and Simpson[13]; their patient was an 11-year-old, apparently healthy schoolboy who suddenly collapsed and died while playing in the street. Post-mortem examination revealed a heart which was very greatly enlarged, weighing 384 grams, due chiefly to thickening of the left ventricle. No congenital anomaly was recorded. All other organs appeared normal. Histologic study showed imperfect transverse and longitudinal striations of the heart muscle fibers due to a "pale foaminess." This appearance was the result of abnormal deposition of glycogen, as demonstrated by the Best carmine stain. The liver showed a similar, but less marked, change. No quantitative chemical studies were made, but the authors stated that the cardiac enlargement was due to glycogen disease.

In our case it is felt that the moderate increase in myocardial glycogen was possibly physiologic and commensurate with the degree of cardiac hypertrophy. At least it can be definitely stated that the increase in the size of the heart was not accounted for by increase in glycogen, as shown in the sections or by chemical analysis. The cause of the hypertrophy was not found; certainly none of the usual factors can account for it. There was no vascular evidence of prolonged hypertension. The absence of scarring or myocardial degenerative changes is evidence against previous rheumatic, diphtheritic, and other infections or "toxic" causes of heart disease. The presence of a four-cusped pulmonary valve could not have been significant, and no other anomalies were found. To consider the "congenital idiopathic" type [1, 5] does not help, and no other etiological factors are apparent. It is remarkable that such marked hypertrophy could exist without some evidence of circulatory embarrassment before sudden death.

SUMMARY

A case of sudden death in an apparently healthy, 11-year-old schoolboy is presented. Marked cardiac hypertrophy was found at autopsy. The cause of the hypertrophy was not discovered.

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Abstracts and Reviews

Selected Abstracts

Rotta, A.: Weight of the Heart and Number of Cardiac Capillaries in Guinea Pigs at Different Altitudes. Rev. argent. de cardiol. **10**: 186, 1944.

A study was made of the heart weight in relation to body weight in guinea pigs born or acclimatized at different altitudes in order to ascertain whether chronic anoxia produces myocardial hypertrophy. In the same animals, the cardiac capillaries per millimeter were counted, and the average diameter and the area of myocardial fibers were measured. The results were compared with identical determinations made in animals living at sea levels.

Chronic anoxia produces some degree of cardiac hypertrophy at altitudes over 3,700 meters. Below this level the heart weight does not differ from that at sea level. At 4,500 M. the heart weight is 30 per cent greater than that at sea level, no difference being observed between native and acclimatized animals. There seems to be a close relationship between severity of anoxia and degree of hypertrophy.

In the cardiac hypertrophy of altitudes the number of cardiac capillaries diminishes as the thickness of the fibers increase, the same as in clinical hypertrophy. The average diameter and the area of myocardial fibers increase together with the increase in heart weight.

AUTHOR.

Palatucci, O. A., and Knighton, J. E.: Short P-R Interval Associated With Prolongation of QRS Complex; A Clinical Study Demonstrating Interesting Variations. Ann. Int. Med. **21**: 58, 1944.

Four cases are reported, exhibiting the syndrome of short P-R interval associated with prolonged QRS complexes in patients with apparently undamaged hearts. Features in common with previously described cases are enumerated. All the variations ascribed to this syndrome are demonstrated, except reversion to normal rhythm after digitalis and quinidine.

Paradoxical atropine effects, a ventricular extrasystole, and recovery from auricular paroxysmal tachycardia are recorded.

Spontaneous and atropine induced T-wave changes are emphasized.

AUTHORS.

Lowe, T. E., and Wartman, W. B.: Myocardial Infarction. Brit. Heart J. **6**: 115, 1944.

Many of the indications of the existence of a myocardial infarct have a ready explanation. Fall of arterial blood pressure is in most cases due either to the amount of muscle tissue destroyed or to the particular muscle involved. Abnormalities in cardiac rhythm and the electrocardiographic changes will be better understood when sufficient data have been compiled relating to the problems of the electrical activity of the heart. Accurate localization of the specific muscle bundles involved may enable us to predict when rupture of the ventricles or even when congestive cardiac failure is to be expected.

The prognosis of a case of myocardial infarction depends as much upon the disease causing the arterial block as it does upon the extent of the muscle damage.

This factor determines the size of the infarct that follows the obstruction of any given vessel and whether or not a recurrence of the episode is to be expected. The varying condition of the coronary arteries is probably the cause of the great variation in the expectation of life after myocardial infarction—a variation from a few moments to some fifteen years.

A knowledge of the behavior of diseased coronary vessels is essential in discussing the surgical procedures advocated for improving the myocardial blood supply in coronary artery disease. These procedures aim at establishing new anastomotic channels between extracardiac and cardiac arteries by placing intercostal muscles or omentum in contact with the pericardium. It is assumed in these procedures that the arterial pressure gradient will force blood from the extracardiac to the cardiac vessels. There is, however, no guarantee that such a gradient will exist. In those cases generally suitable for operative interference the one deficient in blood supply will frequently be deep in the ventricular wall. It is then very doubtful if a satisfactory pressure gradient will exist to transfer any quantity of blood to the heart, and it is possible that the flow will be in the opposite direction. This unpredictable factor probably causes the very variable results that follow these surgical procedures.

AUTHORS.

Stokes, W.: Nicotinic Acid in the Treatment of Angina Pectoris. Brit. Heart J. 6: 157, 1944.

Changes in the electrocardiogram of cardiac ischemia in man, following the administration of nicotinic acid, suggest that the drug can improve coronary blood flow; but this only results from a dosage large enough to produce peripheral flushing, which in itself is an uncertain and unpleasant effect.

In a controlled clinical trial no improvement resulted from the oral administration of nicotinic acid in moderate dosage, either in the prevention or relief of angina, and nicotinamide in larger doses failed to give better results.

Once again glyceryl trinitrate has shown that it has no equal in the treatment of angina pectoris, and nicotinic acid has no claim to routine use in this complaint.

AUTHOR.

Levine, S. A., and Likoff, W. B.: Some Notes on the Transmission of Heart Murmurs. Ann. Int. Med. 21: 298, 1944.

Numerous simple questions concerning the production and propagation of murmurs remain unanswered.

We believe that the velocity of blood flow through the cardiac chambers and great vessels is one important factor in the production of murmurs and in determining their intensity.

Other factors, such as the amount of residual blood in cardiac chambers, the proximity of the heart and great vessels to the chest wall, and the respiratory cycle may influence the presence or absence of murmurs.

The gradation of systolic murmurs from 1 to 6 is important in attempting to estimate their significance, for those of grade 3 intensity, or louder, are never observed in normal individuals, whereas those of grade 1, and occasionally grade 2, are found where there is no evidence of cardiac or other disease.

The detection of murmurs over the olecranon process even with the blood pressure cuff inflated above the systolic pressure level, proves that murmurs are transmitted through bone.

The transmission of an aortic diastolic murmur to the skull, and of the systolic murmur of ventricular septal defect to the carotid area proves that murmurs are not propagated with the blood stream, for the blood flow in these circumstances is in the opposite direction.

Systolic murmurs after effort occur in normal individuals. The production or accentuation of such murmurs after exercise, therefore, cannot be used as a diagnostic test.

There are several mechanisms involved when murmurs are influenced by respiration. All faint murmurs, organic or functional, may disappear with a deep inspiration. In some instances extracardiac systolic murmurs may be louder, and in others fainter, with a deep expiration.

The current teaching about propagation of murmurs needs revision.

These considerations are important in the examination of selectees for military service.

AUTHORS.

de los Reyes, R. P., de la Torre, H., Labourdette, J., and Junco, J. A.: Rheumatic Cardiopathies in Cuban Children. Arch. de med. inf. **13**: 3, 1944.

The authors refer to the incidence and importance of rheumatic cardiopathy among Cuban children, which, though relatively less numerous than in the cold countries, constitutes the greatest calamity children's hearts suffer with acquired cardiopathies.

The study is based on 100 children, 50 boys and 50 girls, chosen from among 200 clinical records of rheumatic children which have been followed up for a long time with a series of electrocardiographic and orthodiagraphic studies, sedimentation rates, and other complementary investigations, pointing out the lesional diagnosis, course of the disease, and treatment used, plus an anatomopathologic study of post-mortem examinations.

The authors have found 30 per cent more incidence in the girls than in the boys; the ages ranged from 5 to 11 years, inclusive. The white race was attacked most often, then the Negro, and third, the mulatto. The poorer and most needy classes offer the greatest number of cases. Mortality has been found to reach 18 per cent.

AUTHORS.

Peete, D. C.: Rheumatic Fever: Diet as a Predisposing Factor. Ann. Int. Med. **21**: 44, 1944.

The author relates evidence which indicates that diet and sunshine are the most important predisposing factors in the causation of acute rheumatic fever. He discusses various climatic conditions which are related.

He believes that the dietary deficiency which closely follows the incidence of clinical rickets alters the individual's immunity to the organism which produces the clinical picture of acute rheumatic fever.

MCCULLOCH.

Rodbard, S., and Katz, L. N.: The Effect of Pregnancy on Blood Pressure in Normotensive and Hypertensive Dogs. Am. J. Obst. & Gynec. **47**: 753, 1944.

The blood pressure in normotensive and especially in hypertensive dogs tends to fall late in pregnancy. The degree of reduction of blood pressure is apparently affected by the size of the litter.

It is possible that the blood pressure decline is related to the low resistance placental circuit which develops during pregnancy. It is also possible that some humoral factor (not involving the fetal kidneys) caused by the maternal endocrine alterations which accompany pregnancy contributes to the blood pressure change and helps to account for the variability in the time at which this blood pressure drop occurs.

Surgical or other traumatic intervention during the latter part of pregnancy appears to predispose to abortion in the dog.

AUTHORS.

Taylor, F. R., and Morehead, R. P.: Spontaneous Complete Rupture of the Aorta Without Dissecting Aneurysm, With Report of a Case Showing a New Physical Sign (Periaortic Friction Rub). Ann. Int. Med. 21: 81, 1944.

Rupture of the aorta is by no means infrequent in the anatomic, as well as the pathologic and clinical literature.

It occurs without the formation of a dissecting aneurysm more often than is usually realized, though the cases with dissecting aneurysm are much more numerous.

The literature on the type of rupture occurring without dissecting aneurysm has been reviewed and an additional case of our own presented, with clinical and pathologic findings.

The gross and microscopic pathology of the condition is discussed.

Certain diagnostic criteria, including a hitherto undescribed physical sign, have been suggested.

The prognosis is hopeless, and treatment is purely symptomatic.

AUTHORS.

Blumenthal, H. T.: Calcification of the Media of the Human Aorta and Its Relation to Intimal Arteriosclerosis, Ageing, and Disease. Am. J. Path. 20: 665, 1944.

The frequency of occurrence and the influence of age, sex, and disease on calcification of the media of the human aorta were studied by means of sections prepared by hematoxylin and eosin staining and by microincineration. The results showed that calcification of the media precedes the formation of intimal plaques; that intimal plaques do not occur without calcification of the media or other medical change such as syphilitic aortitis, or marked connective tissue infiltration of the media; and that within a single aorta medial calcification is probably more intense in the immediate vicinity of an intimal plaque than elsewhere. In a few observations it was noted also that calcification of the human aorta was more pronounced in the abdominal than in the thoracic portion of the aorta.

Calcification of the media of the aorta was shown to be primarily a function of age and was not influenced by sex and various chronic infectious diseases. However, specimens from hypertensive persons between the ages of 30 and 60 years showed considerably more medial calcification than did the "controls." Of 42 cases of syphilitic aortitis, 33 showed no medial calcification, and 9 showed only slight calcification of the media.

The relationship between calcification of the media of the human aorta and the loss of elasticity and contractility with age, as well as the possible relationship of these changes to the formation of intimal plaques, is discussed.

AUTHOR.

Weinstein, J.: "Atypical" Coronary Disease in Young People. Ann. Int. Med. 21: 252, 1944.

Ten cases presenting cardiac manifestations and characteristic electrocardiographic variations suggestive of an unusual type of cardiac infarction are presented.

The patients ranged in age between 20 and 37 years, the average being 28.4 years; 60 per cent of the group were Negroes.

All cases gave a history of upper respiratory infections; four of the cases had joint disturbances; five of eight of the cases had high antistreptolysin titers. None had leucocytosis or polynucleosis, but all had rapid red cell sedimentation rates.

The electrocardiographic variations were characterized by T-wave changes with both anterior and posterior wall type of localization, occasional RT changes, and the consistent absence of QRS abnormalities.

All the cases improved clinically. The electrocardiograms reverted to a normal pattern in six of the cases and in three the changes improved considerably with the probability that they would in time revert to normal.

The upper respiratory infections, the occasional joint disturbances, and the high antistreptolysin titers suggest a rheumatic type of infection.

There is general agreement on the occurrence of coronary arteritis in rheumatic infections. Acute inflammatory arteritis characterized by fibrinoid degeneration and late fibrotic changes has been demonstrated. Cases of our series fit into both types clinically.

AUTHOR.

Lewes, D.: Pulmonary Embolism: The Clinical and Cardiographic Progress of a Case. Brit. Heart J. **6**: 161, 1944.

A case of pulmonary embolism with acute cor pulmonale is described. A severe degree of cor pulmonale developed in the absence of radiological evidence of pulmonary infarction.

Emphasis has been placed on the value of triple rhythm, from the addition of the third heart sound, in the diagnosis of suspected cases of pulmonary embolism.

Radiographic evidence of distension of the right auricle and right ventricle is related to the onset and duration of the cardiographic changes. Inversion of the T wave in CR_1 is probably the most sensitive of the cardiographic indices of right ventricular failure. The value of this change and of findings in lead CR_7 in the diagnosis of acute cor pulmonale from posterior cardiac infarction is confirmed.

AUTHOR.

Brown, J. W., and Hampson, F.: Temporal Arteritis. Brit. Heart J. **6**: 154, 1944.

A case has been described in which the clinical and pathologic findings are those of an arteritis of the temporal arteries. Perusal of the reports of similar cases suggests that temporal arteritis is but a local manifestation of a general disease of the arterial tree.

AUTHORS.

Smith, C. C., Zeek, P. M., and McGuire, J.: Periarteritis Nodosa in Experimental Hypertensive Rats and Dogs. Am. J. Path. **20**: 721, 1944.

Periarteritis nodosa was found at autopsy in twenty-six of sixty-two rats and four of eight dogs which had been made hypertensive by wrapping their kidneys with silk. No evidence of these lesions was found in groups of control animals.

In animals presenting periarteritis nodosa at autopsy, the monthly mean blood pressure levels had been higher than in animals in which no periarteritis nodosa was found. This higher level had been manifested within one month after the production of perinephritis and had been maintained throughout the six months of observation.

Suppurative lesions were common in the experimentally produced perinephric membranes.

A review of the literature revealed no report of the occurrence of periarteritis nodosa in animals in which the kidneys and the blood pressure were proved to be normal.

In the present series of hypertensive animals the two observed differences between those which had and those which did not have periarteritis nodosa were, in the former: higher mean blood pressure levels, and more frequent and more extensive suppurative lesions around the kidneys.

AUTHORS.

Rhode, C. M.: Studies on the Effects of Posture in Shock and Injury. Ann. Surg. **120:** 24, 1944.

The effect of postural change on thirty patients with various degrees of injury is described.

Vasomotor instability was demonstrated in injured patients; this was not present in normal controls and disappeared in injured patients when they returned to normal.

Different effects were noted in response to the head-up or the foot-up position in mild and severe injury or hemorrhage.

Some of the beneficial effects of the foot-up position in the treatment of shock or potential shock as well as some of the adverse effects observed in injured patients in the head-up position are described.

AUTHOR.

Beck, C. S.: Operation for Aneurysm of the Heart. Ann. Surg. **120:** 34, 1944.

The author describes an operation for repair of aneurysm of the left ventricle of the heart. The operation consists of grafting a segment of fascia lata or perietal pericardium over the aneurysm for the purpose of preventing its rupture. The purpose of this procedure is the deliberate reduction of cicatrix to support a dilating heart and also to prevent rupture of an aneurysm of the heart.

MCCULLOCH.

Neuhof, H.: Infected Dissecting Aneurysm of the Iliac Artery Following Arteriovenous Fistula of the Femoral Vessels. Ann. Surg. **120:** 41, 1944.

Severe grades of dilatation of the proximal artery in cases of arteriovenous aneurysm of the popliteal or femoral vessels should be treated by excision of the dilated artery. In the presence of infection within the ectatic artery, excision is imperative.

AUTHOR.

Schindel, L. E., and Braun, K.: The Place of Foliandrin Within the Group of Cardiac Glucosides. Brit. Heart J. **6:** 149, 1944.

The pure glucoside foliandrin isolated from the Palestinean oleander bush (*Nerium oleander*) distinguishes itself very definitely from principles so far isolated from various oleander species. Apart from other chemical as well as physical characteristics, it could be shown by means of continuous electrocardiographic tracings from a cat's heart, that upon intravenous administration its action is identical with that of the principles belonging to the group of strophanthin (ouabain) gluco sides and the drug should therefore be considered a "strophanthinoid." In contradistinction to strophanthin, it displays its full cardiac activity upon peroral administration.

AUTHORS.

Deyrup, I. J.: Circulatory Changes Following the Subcutaneous Injection of Histamine in Dogs. Am. J. Physiol. **142:** 158, 1944.

Subcutaneous injection of 3 to 12 mg. histamine base per kilogram in unanesthetized and etherized dogs resulted in a characteristic circulatory disturbance which differed markedly from traumatic shock in the clinical symptoms produced, in the far greater hypotension, and in the absence of definite blood volume reduction as an etiological factor. Change in blood volume in histamine shock under these conditions resulted from a moderate increase or decrease in plasma volume, and increase in calculated red cell volume, which may have resulted from mobilization of cells from the spleen and other blood depots.

AUTHOR.

Book Reviews

ESCLEROSES VALVULARES CALCIFICADAS: By Dr. Roberto Menezes de Oliveira. Tipografia do Patronato, Rio de Janeiro, 1943, 154 pages, 67 illustrations.

This excellent monograph is based on the study of one hundred cases at the Peter Bent Brigham Hospital in Boston. The first part is devoted to the anatomy and histology of the heart valves. The second part is a pathologic study of calcification of the cardiac valves, with a discussion of twenty-five autopsy cases. The third part comprises observations on one hundred cases from the roentgenologic point of view. The fourth part is a clinical study. A short description of the cases and an extensive summary, in both Portuguese and English, close the book.

Some of the conclusions deserve to be extensively quoted. The posterior part of the *annulus fibrosis* of the mitral valve is a frequent site of calcification. The latter, however, often appears at points of functional strain, such as the valvular insertions. Calcification of the valve ring is always accompanied by a lesion of the valve, usually of a fibrotic type. Purely degenerative lesions of the ring, on the other hand, may be more limited. Calcification of the valve ring is more common in women than in men. Degenerative, calcific lesions of the valves are almost always caused by endocarditis, but calcific lesions of the valve rings may be due to either endocarditis or arteriosclerosis.

Calcification limited to the aortic ring is rare. It may be caused by both inflammatory and degenerative lesions (either ascending or descending). It gives no signs or symptoms, and is recognized roentgenologically only with difficulty.

The differentiation between purely degenerative lesions and arrested, mild endocarditic lesions can be made only by means of serial sections, and even then may be impossible. The two lesions, moreover, may be either associated or superimposed. Impairment of cardiac conduction is rarely caused by extension of degenerative processes to the septum.

Roentgenologic diagnosis of calcification of either the valves or their rings is easy, but often incomplete. The diagnosis is more difficult in cases in which the lesions are mixed.

Data are given which can be used for the roentgenologic differentiation of calcification of the *annulus fibrosis* from that of the aortic valves. Means of differentiating, roentgenologically, between aortic and mitral valve calcification are also given.

Calcification of the mitral valve is pathognomonic of mitral stenosis only when it is limited to the leaflets, in which case it is always the result of endocarditis. Valve calcification is a sign of valvular disturbance, usually stenosis, when it is of endocarditic origin. Degenerative processes rarely disturb the function of the mitral valve, but may cause aortic stenosis.

Roentgenologic study of valvular calcification has illuminated many interesting phenomena of cardiac dynamics. Slight mitral stenosis and regurgitation were found in eleven cases, and slight aortic stenosis and regurgitation in only one case, out of twenty autopsy cases of purely arteriosclerotic, but extensive, lesions of the cardiac valves.

Excellent sketches and adequate, or good, roentgenograms are presented.

ALDO LUISADA.

PHYSIOLOGY IN HEALTH AND DISEASE: By Carl J. Wiggers, M.D., D.Sc., Professor of Physiology, School of Medicine, Western Reserve University. Fourth edition, Lea & Febiger, Philadelphia, 1944, 1174 pages, 247 illustrations, $10.00.

The editors of the AMERICAN HEART JOURNAL asked the reviewer to cover only the part of this well-known textbook which is concerned with cardiovascular physiology, to which Section V, which comprises 285 pages, is devoted.

Dr. Wiggers' many investigations in this field are well known, and a careful summary of this work, together with his views on the work of others, is given. The contents have been brought rigorously up to date, over 1,000 new references have been added, and especial attention has been given to topics, such as shock and hemorrhage, brought to the front by the war. Although some material previously included has been omitted to save space, the omissions have been well chosen. The style is perhaps somewhat obscure in places, but is usually clear and vigorous; the reviewer especially liked the analogy between the vectors whose resultant is the electrocardiogram and the efforts of two teams of men pulling in various directions upon a rope. Indeed, the reviewer read the section with no little profit to himself.

There have always been two schools of physiologic thought. The first insists on methods of the utmost refinement, but, in order to apply them, must turn to animal experiments and often be willing to sacrifice normality by the use of anesthetics and elaborate operative procedures. Inasmuch as this school possesses a strong faith in the uniformity of nature, it does not hesitate to apply the results obtained in such animal experiments to human problems. The second school prefers to solve problems related to man by working on man himself, or on animals which are disturbed as little as possible, both physiologically and psychologically. But, in order to accomplish this aim, the members of this school must be content to employ methods far cruder than those of the first group. Knowledge has been advanced by both schools.

In his philosophy of science Dr. Wiggers is a charter member of the first school, whereas the reviewer belongs to the second. Therefore, the latter would prefer to have medical students presented with less generalization from the results, and with more details concerning the situation under which observations quoted were made. In acute animal experiments, the type and depth of anesthesia, the extent and duration of the operative procedure, and the species of animal play a part in the results obtained. Although medical students taking Dr. Wiggers' laboratory course would surely realize the hazards involved in the interpretation of results obtained in such animal experiments, and although certain difficulties are pointed out in this textbook, the general tenor of the reasoning is to emphasize the method of recording, and, if this is satisfactory, to draw a conclusion which encompasses the whole mammalian field. The reviewer believes that the relation between the rising school of physiologic clinicians and the group whose lives have been devoted to elaborate animal experimentation would be sounder if the difficulties inherent in the interpretation of such experiments were given more emphasis in physiologic textbooks and in the teaching of medical students.

ISAAC STARR.

PRE-EXCITATION, A CARDIAC ABNORMALITY: By Richard F. Öhnell, translated by Ulla Schött, P. A. Norstedt & Söner, Stockholm, 1944, 167 pages, 30 illustrations.

Pre-excitation is a term used by the author to mean that the ventricular part of the heart is subjected to an additional excitatory spread, setting in shortly before the start of the regular excitation wave. This is the phenomenon reflected in electrocardiograms by the combination of a short P-R interval and a prolonged, aberrant QRS complex.

This monograph, which, it is announced, is to be published as a supplement to *Acta Medica Scandinavica*, has been excellently translated into English. The author

reveals a comprehensive and accurate knowledge of the literature. He has made various types of observations on seventy cases. Perhaps the most interesting is the demonstration in one case of a "peripheral" muscular band connecting the left auricle and left ventricle. The muscle in this band appeared to be nonspecialized, and thus resembled the multiple connections between the right auricle and right ventricle found by Wood, Wolferth, and Geckeler in a case with a similar electrocardiographic anomaly. Another interesting observation is what appeared to be a familial incidence in two families.

The author concludes that the abnormality of mechanism in most cases is that suggested by Wolferth and Wood, in 1933, to the effect that the cardiac behavior could be accounted for by assuming that the excitatory process is transmitted from auricles to ventricles via *both* the normal channels and an accessory conduction tract. He believes, however, that, in certain cases, the abnormality may be acquired, and that mechanical stimulation of a ventricle by auricular activity might be the underlying mechanism.

This monograph is unhesitatingly recommended to all who are interested in the anomaly of short P-R interval and prolonged aberrant QRS complex. The only serious criticisms this reviewer has to make are as follows: (1) The method of presentation, by which, in each of the nineteen chapters, all with a summary, a single aspect of the subject is discussed, leads to much repetition. (2) The author has not utilized chest leads to the fullest advantage in his study of the subject. By their use, provided the exploring electrode is placed over both the right and left sides of the precordium, the fundamental differences in mechanism between intraventricular conduction defect and this anomaly are so clearly displayed that confusion between the two would be difficult.

CHARLES C. WOLFERTH.

Erratum

On page 269 of the August, 1944, issue of THE JOURNAL, in a footnote to his review of *Hipertension Arterial Nefrogena*, Dr. Aldo Luisada stated that Professor B. A. Houssay has been working for the Rockefeller Foundation since his dismissal by the present governmental regime of Argentina. Later it was learned that Professor Houssay is working in a private institute in Argentina. Some of his collaborators have obtained apparatus and assistance through the Rockefeller Foundation.

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